



PHD

Autistic Characteristics in Adults with Epilepsy

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Autistic Characteristics in Adults with Epilepsy

SallyAnn Rose Wakeford

A thesis submitted for the degree of Doctor of Philosophy

University of Bath
Department of Psychology
November 2012

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Autistic Characteristics in Adults with Epilepsy

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SallyAnn Wakeford
University of Bath
April 2012

Abstract

The prevalence of autism spectrum disorders [ASD] in epilepsy is approximately 20%-32%, with previous research reporting high rates of under-diagnosis of ASD in epilepsy. Current psychological assessments were adapted to provide epilepsy-specific measures of behaviour, which increased validity by addressing specific methodological problems highlighted by several researchers. The initial experiments provided a comprehensive investigation of autistic traits and characteristics in a heterogeneous group of adults with epilepsy without any ASD diagnosis to quantify the extent to which autistic characteristics are related to seizure activity. Adults with epilepsy showed higher autistic traits and impaired social responsiveness while systemizing and empathising abilities remained intact. Further, autistic traits and impaired social responsiveness increased again during seizure activity. Social responsiveness positively correlated with anti-epileptic drug [AED] control. Adults with epilepsy and seizure remission demonstrated significant improvements in restricted, repetitive behaviours compared to adults with current epileptic seizures. Together, these results demonstrate a relationship between seizure activity and autistic characteristics, and are consistent with previous suggestions that AEDs may mask autistic characteristics. The impaired social skills and communication are consistent with research suggesting that the pathogenesis of epilepsy may disrupt social functioning. However, whether this can be directly attributed to social cognitive deficits remains uncertain. The main research addresses this uncertainty by conducting three experiments to assess the Somatic Marker Hypothesis and the mechanisms which underpin it. The rationale is to establish whether this is a valid explanatory model for disrupted neurobiological factors implicated in social cognitive processing. This hypothesis is appropriate for investigating adults with epilepsy, some who may have developed typical social abilities in early life before epilepsy onset. Results from the IOWA Gambling Task demonstrated that adults with epilepsy had impaired decision making abilities compromising somatic marker formation, crucial for social cognition. However, this deficit occurred in the absence of other socio-emotional and memory impairments. In conclusion, adults with epilepsy have a higher rate of autistic characteristics, and their social difficulties may be associated with compromised somatic marker formation. Future research needs to determine the heritability of these autistic traits and characteristics.

List of Abbreviations

AD	Autistic Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AED	Anti-Epileptic Drug
ANCOVA	Analysis of Covariance
AQ	Autism Quotient
AR	Autistic Regression
AS	Asperger's Syndrome
ASC	Autism Spectrum Condition
ASD	Autism Spectrum Disorder
BAP	Broader Autism Phenotype
CEFT	Children's Embedded Figures Test
DV	Dependent Variable
EDT	Executive Dysfunction Theory
EEG	Electroencephalogram
EF	Executive Functioning Theory
EMB	Extreme Male Brain Theory
FER	Facial Emotion Recognition
FSIQ	Full Scale Intelligence Quotient
FSIQ-2	FSIQ calculated from 2-subtests of the WASI
HFA	High-functioning Autism
HS	Hippocampal sclerosis
IGE	Idiopathic Generalised Epilepsy
IGT	IOWA Gambling Task
ILAE	International League Against Epilepsy
IP	Intuitive Physics Test
IQ	Intelligence Quotient
IV	Independent Variable
JME	Juvenile Myoclonic Epilepsy
LKS	Landau Kleffner Syndrome
LTLE	Left Temporal Lobe Epilepsy
M:F	Male to female ratio
MRIQ	Matrix Reasoning Intelligence Quotient
ms.	milliseconds
MTL	Medial Temporal Lobe
MTLE	Medial Temporal Lobe Epilepsy
mTLE	Mesial Temporal Lobe Epilepsy
NICE	National Institute for Health and Clinical Excellence
OCD	Obsessive Compulsive Disorder
PDD-NOS	Pervasive Developmental Disorder, Not-Otherwise Specified
QOL	Quality of Life
RT	Response Time
RTLE	Right Temporal Lobe Epilepsy
RWL	Related-Word List
SCR	Skin Conductance Response
SD	Standard Deviation
SMH	Somatic Marker Hypothesis
TLE	Temporal Lobe Epilepsy
ToM	Theory of Mind
TSH	Task Support Hypothesis
UoB	University of Bath
UoB-Ethics	University of Bath Department of Psychology Ethics Committee
UWL	Unrelated-Word List
VIQ	Verbal Intelligence Quotient
vmPFC	Ventromedial Prefrontal Cortex
WAIS-R™	Wechsler Abbreviated Scale of Intelligence Revised
WCC	Weak Central Coherence Theory

Terms

The definitions below were formulated by the International League Against Epilepsy (ILAE), 2005.

Epilepsy

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al., 2005, p.470).

Epileptiform Discharge

An epileptiform neuronal discharge is a discharge which resembles epilepsy or the manifestations of epilepsy, and is associated with an increased risk of seizures (Schachter, 2004).

Epileptic seizure

An Epileptic seizure is a transient occurrence of signs and symptoms presumed to result from an abnormal and excessive neuronal activity in the brain (Fisher et al., 2005, p.470). Epileptic seizures are clinical manifestations of epilepsy.

Epileptic event

In this thesis, all references to an epileptic event are referring to any epileptic seizure activity, unless stated otherwise.

Epilepsy syndrome

A complex of signs and symptoms that define a unique epilepsy condition (Engel, 2001).

Post-ictal stage

The postictal stage of epilepsy is the abnormal state occurring between the end of an epileptic seizure and the return to a baseline condition, which can continue for up to 48 hours (Fisher & Engel, 2010).

Seizure

In this thesis, all references to seizures are referring to epileptic seizure activity, unless stated otherwise. According to the ILAE, “seizure presentation depends on location of onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, sleep-wake cycle, medications, and a variety of other factors. Seizures can affect sensory, motor, and autonomic function: consciousness; emotional state; memory; cognition; or behaviour. Not all seizures affect all these factors, but all influence at least one. In this context, sensory manifestations are taken to include somatosensory, auditory, visual, olfactory, gustatory, and vestibular senses, and also more complex internal sensations consisting of complex perceptual distortions” (Fisher et al., 2005, p.471).

Chapter 1

General Introduction

*“José had lived for fifteen years in a guarded, closed world –
in what Bruno Bettelheim in his book on autism called the ‘empty fortress’.
For fifteen years he scarcely emerged from the house,
ostensibly because of ‘intractable seizures’.
What then was José, I had to ask myself. What sort of being?
What went on inside him? How had he arrived at the state he was in?
And what state was it - and might anything be done?”*

Oliver Sacks (1985, p.220)

1.1 Overview of this Introduction

This chapter provides the reader with an introduction to this research project which investigates autistic characteristics in adults with epilepsy, and the rationale supporting this investigation. This research project has two aims with regard to investigating autistic characteristics in adults with epilepsy. Firstly, to establish the extent to which these characteristics are associated with *Seizure Auras*. Seizure auras are unilateral ‘focal epilepsy’, denoting the ictal onset of epilepsy. Anecdotal evidence suggests that cognition and behaviour during focal seizure activity is consistent with some patterns found in those with autism spectrum disorders [ASD]. This research initially sets out to quantify the extent to which autistic characteristics are related to Seizure Aura activity. A new method of psychological assessment will be employed to assess adults with epilepsy without any clinical diagnosis of an autism spectrum disorder. The quantitative measurement of autistic traits with respect to the semiology of the epilepsy stages of seizure auras will be addressed.

Secondly, having established this relationship, pertinent theoretical models will be employed from the ASD literature to better understanding the psychological underpinnings of these characteristics, and to undertake theoretical research to establish a relationship. Relevant tasks were selected to evaluate the explanatory power of these models for adults with epilepsy. In addition, the implications for theories

of autism spectrum disorders in those with focal epileptic activity will be discussed. Ultimately this research seeks to define this relationship and provide a greater understanding to inform those involved in diagnosis and therapeutic intervention.

1.1.1 Outline of Thesis

To address these two aims, the thesis has the following outline:

Chapter 1 provides a general introduction to the rationale of the research and its importance, and the concepts discussed throughout the thesis. Chapters 2 and 3 define the epilepsy and autistic conditions. Chapter 4 provides a thorough literary review of the co-morbidity, and cognition and behaviour related to each condition, and provides a discussion of current methods of assessment for individuals with epilepsy, including the validity of such measures. Initial exploratory experiments will be conducted to assess core autistic traits and characteristics in Chapters 5 and 6 (respectively). These exploratory experiments seek to address the first research aim, which is to establish the extent to which autistic characteristics are associated with Seizure Auras. The first experiment, Experiment 1, will investigate Autistic Traits. However, as it is necessary to show that only autistic traits are found in adults with epilepsy, this will be followed by Experiment 2, which will investigate Empathising and Systemizing abilities. As the spectrum of autistic traits is also found in the wider general population and includes individuals who may not have ASD, the exploratory Experiments 3 and 4 will investigate specific core characteristics of ASD. Experiment 3 will investigate social responsiveness, as a quantitative measure of severity of social impairment. Experiment 4 will investigate restricted repetitive behaviour in epilepsy. It was necessary to do 4 initial experiments as there was a lack of previous research in this area, and these experiments employed a new method of psychological assessment.

Continuing from the evidence provided from the first research aim, Chapter 7 starts to address the second aim of this research project. This is to employ pertinent theoretical models from the ASD literature to provide a better understanding of the psychological mechanisms underpinning the patterns of cognition and behaviour revealed by the exploratory experiments, and to evaluate the explanatory power of these models.

There exists a strong relationship between childhood epilepsy and autism during which the effects of temporal lobe epilepsy on early brain maturation has been implicated in disruption to social cognitive functioning (Shaw et al., 2004). However, this association implies that acquired epilepsy in adulthood after a normal brain development cannot share a relationship with autism, since ASD is considered to

be a developmental life-long condition. Further, many of the core characteristics of ASD found in adults with epilepsy can be explained by well-documented research in the domains of memory, executive functioning and language in this population. However, the defining core characteristic of ASD, social cognition has not yet been well studied in adults with epilepsy which Jokeit argues is astonishing, given the remarkable overlap of epilepsy with anterior brain structures implicated in social cognition (Jokeit, 2010). This thesis examines suggestions that these social difficulties are under-recognised, and explores the genuine uncertainty of whether they really can be attributed to the social cognitive consequences of having epilepsy.

The primary theoretical model employed to address this aim will be the Somatic Marker Hypothesis. Compromised somatic marker formation is considered to hinder social interaction, as they are particularly important in the social domain (Adolphs, 2001). The rationale for exploring somatic markers is that compromised somatic marker formation in adults with epilepsy may explain impairments in the social domain. Two further tasks were employed to determine what mechanisms underpinning somatic markers may compromise their formation in adults with epilepsy. These two tasks are the Task Support Hypothesis [TSH], and a Face Emotion Recognition task [FER]. A decision making task, the IOWA Gambling Task [IGT], explored somatic marker formation as a guide to decision making under ambiguity.

Continuing from Chapter 7, Chapter 8 identifies the participant sample clinical and demographic characteristics, and ethical considerations for the experiments. Experiments 5a and 5b replicated the Task Support Hypothesis [TSH] developed by Bowler and colleagues (Bowler, Matthews, & Gardiner, 1997). Experiment 5a explores the effect of categorisation in a free recall task. Experiment 5b explores encoding and explicit and implicit memory recall, to look for specific memory patterns that have been previously associated with ASD (ibid).

Chapter 9 investigated the contribution of the amygdala to the formation of somatic marker associations in Experiment 6, which employs a face emotion recognition task [FER] to provide a more in-depth assessment of emotion recognition and emotion intensity recognition (Harmer et al., 2003). Experiment 7 quantitatively measured decision making in adults with epilepsy to explore the formation of somatic markers, by employing the IOWA Gambling Task [IGT] (Bechara, Damasio, Damasio, & Anderson, 1994).

Chapter 10 discusses the findings from Experiments 1-7, with reference to the overall research question which explores evidence for impaired decision making that may underlie social cognitive difficulties in adults with epilepsy. Patterns of decision making on the IGT and their relationship to similar patterns found in adults with ASD will be discussed in relation to autistic characteristics. The findings of higher autistic traits (AQ) and decreased social responsiveness (SRS-S) in adults with epilepsy contrast with a lack of compromised emotional recognition measured by FER, provide an interesting contradiction. However, one important consideration is the effect of AED medication on cognitive functioning which may improve some abilities, such as repetitive and rigid behaviours, and socio-emotional functioning. Finally, the limitations of this research project will be acknowledged.

1.2 Why research autistic characteristics in epilepsy?

Epilepsy shares a high co-morbidity with autism spectrum disorders [ASD]. Investigations into autistic characteristics have been severely neglected in those with epilepsy, and the specificity of these autistic-like behaviours remains controversial, and therefore poorly defined. To date, no research has been conducted quantitatively measuring autistic traits employing the Autism Quotient, or measuring autistic characteristics such as social responsiveness, repetitive behaviours, or systemizing abilities in epilepsy. This research project aimed to fill this gap in the research. This led to an in-depth investigation for the findings that were uncovered.

This research is important because it has only recently been recognised that epileptic activity without convulsive seizures cause cognitive impairments and behavioural disturbances that can be the *only* symptom of an epileptic disorder (Deonna & Roulet-Perez, 2006). At the same time, increasing evidence suggests a direct role for these seizures contributing to cognitive and behavioural disturbances. Recent attention has focused on the high presence of epileptiform discharges in individuals with ASD. Epileptiform discharges do not diagnose epilepsy, but these neuronal discharges can be a symptom of the underlying brain pathology of epilepsy (Schachter, 2004). Some evidence has revealed that frequent epileptiform discharges in early childhood can lead to a permanent ASD type condition, while the epileptiform discharges subsequently are resolved (Besag, 2009). As a consequence, there has been much debate about the extent to which they may be associated with a manifestation of autistic disorders in children with epilepsy. However in contrast, these behaviours can improve after treatment, and in some individuals with co-morbid diagnosis of epilepsy and ASD, management of seizures have been related to the disappearance of autistic behaviour (Yasuhara, 2010). However, this association does not imply that epileptic activity is a cause for ASD. Each condition is independent with different treatment pathways. In addition, these impairments may be particularly hidden in children, in whom diagnostic accuracy of epilepsy is a

particular problem (Baise-Zung, Guilhoto, & Grossmann, 2006; Park et al., 2009; Parra, Iriarte, & Kanner, 1999; Sander & Neligan, 2011). This thesis questions the way in which seizures affect daily behaviour, arguing that for some adults these symptoms can be severe and hidden. This raises implications for how epileptic behaviour is perceived, how adults with epilepsy should be assessed, managed, and what therapeutic interventions should be available.

At present, there is still much debate as to whether the relationship between epilepsy and ASD is causal, coincidence, co-morbid or a consequence. However, while it is unclear if ASD are under-diagnosed in adults, there is some evidence suggesting that ASD are routinely suspected to be under-diagnosed in children (Saemundsen, Ludvigsson, Hilmarsdottir, & Rafnsson, 2007; Steffenburg, Steffenburg, & Gillberg, 2003). However, it could be equally argued that epilepsy merely mimics autism disorders due to brain structure similarities in Medial Temporal Lobe Epilepsy [MTLE], which has a focal onset in the inner temporal lobe. While there are characteristics common to both MTLE and ASD, this does not provide explanations for autistic characteristics suspected in other types of epilepsy. More recently, a study by Voets and colleagues (2011) has identified a common neuro-developmental factor which may play an important role in the development of TLE. The researchers state that this suggests a common neuro-developmental phenotype for TLE. This is important because temporal lobe epilepsy is the most common epilepsy type with focal seizures, which have been found to be twice as common as generalised seizures in adults over 24 years of age (Hauser, 1993). Further, a high rate of seizure auras are found in adults with epilepsy, and these share similarity with TLE as they can originate in the hippocampus and the adjacent limbic system (mesio-temporal structures) including the amygdala. Therefore it is appropriate to study autistic characteristics in adults in this research project.

1.3 Research rationale

There are many reasons to suspect autistic characteristics in individuals with epilepsy, but the current gap in the literature means that there is no comprehensive and systematic study of these characteristics in an adult population. Epilepsy is a ‘hidden’ or ‘invisible’ condition, as symptoms may not always be apparent except during a seizure. Subtle cognitive and behavioural disturbances that result from epilepsy are of central significance and often remain unrecognised (Aicardi, 1999). Carrying a hidden condition can lead to social misunderstandings, with the person’s misbehaviour and poor social conduct being misinterpreted by others. Social communication problems can lead to difficulties forming social relationships, social exclusion, impaired self-esteem, anxiety, depression, and higher incidences of suicide (Jacoby & Austin, 2007). The psychological consequences of epilepsy can be

severe and of more importance than the epilepsy itself, leading to psychological suffering (Baker, Aldenkamp, & Meador, 2004).

The focus of medical professionals can often be to encourage patients to participate more in social activities to combat stigma, there is some belief that promoting self-management of a person's 'epilepsy identity' will resolve social difficulties. However, in the absence of a thorough and systematic investigation into the nature of these social and behavioural difficulties, they are at risk of being mislabelled and untreated. The rate of under-diagnosis of ASD in childhood epilepsy suggests that for some individuals, symptoms are still hidden. The current advice by one prominent Epilepsy UK Organisation given to parents of children with epilepsy states that it is rare for behavioural problems to be a direct result of epilepsy and it is a myth that there is an epileptic personality (The National Society for Epilepsy, 2010). However, many reports of behavioural disturbances related to epilepsy are anecdotal, and do not include validated measures of behaviour. This research is important, because individuals with epilepsy cannot be helped if their behavioural difficulties go unrecognised. As such, an investigation in autistic characteristics in adults with epilepsy is worthwhile and valuable. A greater understanding of these behaviours could lead to better targeted therapeutic and medical intervention. The evidence for co-morbidity of cognition and behaviour are discussed in the literature review in Chapter 4, to evaluate the extent to which underlying processes and structures may be involved.

1.4 Main Research Rationale

Despite evidence that anti-epileptic medication improves autistic characteristics, the question of whether actual social behaviour is a reflection of impaired social cognitive abilities in adults with epilepsy, is largely unanswered (McCagh, Fisk, & Baker, 2009; Di Martino & Tuchman, 2001). There are two possible explanations for social difficulties and differences in adults with epilepsy. The main research aim is to investigate whether social behaviour in adults with epilepsy associated with autistic characteristics are a result of impaired somatic marker formation which may compromise social cognitive functioning. The specific research question is: *is the formation of somatic markers compromised in adults with epilepsy?*

The main research experiments will investigate decision making to explore whether somatic markers may be related to social cognitive differences which may account for these characteristics. The Somatic Marker Hypothesis proposes that somatic markers guide social interactions and enable individuals to learn from their previous social interactions (Damasio, Everitt, & Bishop, 1996). Experiment 7 quantitatively measured decision making in adults with epilepsy to explore the

formation of somatic markers, by employing a decision making task, the IOWA Gambling Task [IGT] (Bechara et al., 1994). A Facial emotional recognition [FER] task will provide an indication of emotional functioning crucial for formation of somatic markers and linked to social cognitive functioning. Importantly, those with ASD are impaired in empathising, which is revealed by poor performance on FER tasks. In addition, as performance on the decision making task depends on intact explicit memory for the formation of somatic markers, several memory tasks will provide a measure of explicit memory, as well as investigating specific memory patterns in individuals with ASD (Guillaume et al., 2009; Gutbrod et al., 2006). These memory patterns have not yet been investigated in adults with epilepsy, and these experiments aim to fill this gap in the research.

1.5 Summary

Although anecdotal evidence and exploratory research experiments have suggested some evidence for social impairments in adults with epilepsy, it could be argued that these impairments are a result of environmental and psychosocial factors. Further investigation is needed to resolve this issue. Therefore, this research project will seek for theoretical explanations by investigating social functioning in relation to the formation of somatic markers, emotion-based biasing signals which guide social interaction. In addition to the decision making task, memory and face emotion recognition will also be investigated. Participants will be recruited primarily from an Epilepsy Charity to test the hypothesis that adults with epilepsy process social information differently to a matched adult control group. The results from this research will produce highly useful information about social cognition in adults with epilepsy, and provide further evidence to the extent of autistic characteristics in this population.

1.6 Contribution

The contribution of this research project will increase understandings which may benefit adults with epilepsy, to inform those involved in diagnosis and therapeutic intervention, and to lead to the development of more specific treatment strategies.

Chapter 2

Epilepsy

“It is like being on a firing range without a blindfold. Watching the marksman enter, stop, slowly raise his gun and gradually press the trigger. The experience causes an increasing intensity of fear, and is an experience I have no control over. Gradually, a churning feeling begins in my stomach which grows stronger and stronger and increases my sense of fear. Panic too, if I cannot get myself into a safe situation before the inevitable occurs and I black out.”

Male aged 35, childhood-onset of epilepsy

2.1 Epilepsy

Epilepsy is one of the oldest recognised neurological disorders, but historically has a contentious history of cultural stigma, unnecessary deaths, unsuccessful surgery, and adverse effects of medication. If left untreated, epilepsy can be life-threatening, and every seizure can be potentially dangerous resulting in brain damage by inducing neuronal death. On the other hand, more recent valuable research has led to better understanding of epilepsy, newer anti-epileptic drugs, and avoidance of past mistakes. According to the ILAE, convulsive activity is not a criterion for epilepsy and several types of epilepsy are non-convulsive, for example neonatal seizures (Doyle, Temko, Marnane, Lightbody, & Boylan, 2010). Epilepsy is a condition which can be either transient or life-long, depending on the syndrome, cause and treatment (Dulac, Nabbout, Plouin, Chiron, & Scheffer, 2007). The prevalence, classification and causes of epilepsy are outlined below. Support for people with epilepsy is inadequate, and fails the National Institute for Health and Clinical Excellence (NICE) guidelines set out in 2004 (APPG, 2007). Research suggests support for people with epilepsy is fragmented and poorly co-ordinated. Therapy for cognitive and behavioural disorders is unsatisfactory, and many individuals simply give up their struggle with the system (Sander, 2004). A hard-hitting report reviewed by the Hansard Committee revealed the human cost of epilepsy and highlighted inadequate services (APPG, 2007). The inquiry concluded that urgent action is essential to treat individuals quickly and accurately.

While the ILAE acknowledges the social consequences of epilepsy, there is a shortage of research investigating social cognition in epilepsy. While it is likely that social difficulties are the result of complex interrelated factors, research has not yet established the extent to which these are a consequence of psychosocial factors or the pathogenesis of epilepsy. Multiple psychosocial factors have been highlighted such as poor self-esteem, stigma and social isolation (McCagh et al., 2009). Equally, it has been established that epilepsy can affect brain structures important for socio-emotional processing, as well as neural networks mediating social cognition that are essential for social behaviour (Schacher et al., 2006). However while this suggests that the pathogenesis of epilepsy may disrupt social cognitive abilities, whether the social difficulties of adults with epilepsy can be attributed to social cognitive deficits still remains uncertain (ibid). This is especially important as there is a high prevalence of ASD in epilepsy of which impaired social cognition is a core and defining characteristic. Social cognitive deficits in ASD can be profound, are found across the spectrum even in adults with high-functioning autism, and have been well-documented since autism was first identified. Where evidence of an epilepsy-autism co-morbidity is found, more research is needed to determine the extent to which these disorders require similar or different treatment pathways.

2.2 Epileptic Seizures

Epilepsy is the most common neurological disorder worldwide (Jacoby et al., 2005). Epilepsy can affect anyone at any age, gender, race and socio-economic background, and the vast majority of individuals with epilepsy can take part in everyday activities. The epileptic seizure activity can cause changes in an individual's movements, behaviour, emotions and senses, and usually lasts for several minutes until brain activity returns to normal. However, it can take several hours for a person to recover after the seizure event. Importantly, the cognitive and behavioural consequences of epilepsy can sometimes be the only symptom. Even so, individuals with epilepsy have a spectrum of self-control behaviours in stressful situations, either to avoid seizure precipitants or to terminate seizures (Spector et al., 2001). An evaluation of the extent of these precipitants by Spector, Cull and Goldstein (2000) found that 52% of adults with epilepsy consciously try to avoid seizure precipitants, and 47% reported some success in doing so, and this increased to 60% of adults who reported seizure warnings. Despite this, if left untreated seizures can potentially be dangerous and lead to negative effects on cognitive functioning. Every year, 1,000 people in the UK die of epilepsy-related causes, 370 of those deaths are children and young adults (Hanna et al., 2002).

2.3 Prevalence rate

The prevalence of epilepsy is the total number of existing cases as a proportion of a population, at a specific time. Prevalence data are supplied by the Joint Epilepsy Council, and are the most recent data available for the UK. The age standardised prevalence rate of epilepsy in the UK is 7.5 per 1,000. This affects one in every 131 individuals, which equates to 456,000 individuals in the UK, and around 60,000 school children (Deacon, 2005). Epilepsy has no geographical, sex, age, racial or social boundaries, although it is most frequently diagnosed in infancy and old age (ibid.).

2.4 Incidence rate

The incidence of epilepsy is based on the number of newly-diagnosed cases of epilepsy as a proportion of a population, at a specific time. In the UK, the current incidence rate of epilepsy is around 0.46 cases per 1,000 of the UK population (Deacon, 2005). This is equivalent to approximately 75 cases of newly-diagnosed epilepsy every day. This is similar to current reported rates in other developed countries. Although developing countries report generally higher incidence rates, socio-economic deprivation has been identified as one predominant factor. Seizures are more commonly found in the newborn neonatal stage of life than at any other time (Glykys et al., 2009). In newborns, seizures are often 'clinically invisible' showing no visible convulsive signs, causing serious damage to the brain (ibid.).

2.5 Diagnosis

According to the ILAE definition and in contrast to definitions of epilepsy in current research, the seizures do not have to be unprovoked, a feature of several prior definitions. In contrast, provoked seizures resulting from an apparent cause such as a brain infection are not considered epileptic (Wiebe, Téllez-Zenteno, & Shapiro, 2008). At least one seizure is required to establish the presence of epilepsy, where there is evidence of an enduring alteration in the brain (Fisher et al., 2005, p.472). The central concept to this definition for diagnostic purposes is an enduring alteration in the brain which increases the likelihood of future seizures. Therefore, a single seizure due to an enduring epileptogenic abnormality would indicate epilepsy, a single seizure in a normal brain would not (ibid., p.472). However, there is no single test that can diagnose epilepsy, therefore diagnosis is based upon a detailed history and eyewitness reports supported by EEG recordings, and an extended period of follow up (Chapman et al., 2011; Sander & Neligan, 2011).

2.6 Misdiagnosis

The diagnosis of epilepsy is often difficult and misdiagnosis is common (Uldall, Alving, Hansen, Kibaek, & Buchholt, 2006). A review of misdiagnosis of epilepsy by Benbadis and by Chapman and

colleagues highlighted multiple factors implicated in misdiagnosis of epilepsy: the provision of epilepsy services; failure to obtain an adequate history; placing inappropriate emphasis on Electroencephalogram (EEG); lack of long-term follow-up; and lack of monitoring long enough to detect epileptic events (Benbadis, 2007; Chapman et al., 2011). Conversely, it is well-reported that specific types of epilepsy in children can often go unnoticed such as absence seizures, or that epilepsy occurring during night time can go unreported (Hoppe, Poepel, & Elger, 2007). Additionally, symptoms of epileptic seizures can be incorrectly related to a psychiatric or associated disorder, leading to under-diagnosis (Chapman et al., 2011). What is required are robust quantitative measures of cognitive and behavioural characteristics associated with specific epilepsy syndromes that can help in the detection of epilepsy, and discriminate epilepsy from non-epileptic seizures and other psychiatric disorders. However, while specific characteristics in individuals with epilepsy have been looked for, evidence so far suggests there is no epilepsy ‘personality’ or type, and that behavioural problems are not a direct result of epilepsy.

EEG has its strengths and limitations. EEG has the ability to determine whether the patient has epilepsy, and where the epileptogenic zone is located. EEG is limited as it only measures epileptic activity if the epileptic seizure is captured during the recording. Routine EEG recording of epilepsy patients do not show epileptiform activity in about 50% of cases (Flink et al., 2002). Various methods are employed to induce seizures in individuals with suspected epilepsy during the EEG recording, which can be unsuccessful. EEG reports on neuronal activity at the time of the recording, and is useful only for distinguishing seizures from non-seizure events during the EEG recording. Of special interest is that not all epilepsies are associated with epileptiform discharges. For example, according to Tononi and Koch, Temporal Lobe Epilepsy [TLE] can be associated slow wave activity similar to those of sleep or anaesthesia rather than to epileptiform discharges (Tononi & Koch, 2008, p.246). Unrealistic expectations of EEG may be one factor for misdiagnosis, but Peake and colleagues warn that an EEG may be supportive of the clinical diagnosis of epilepsy but should not be used in isolation (Peake, Notghi, & Philip, 2006, p.492). According to Park and colleagues, the diagnostic accuracy of conventional EEG in children is approximately 50% at best (Park et al., 2009). More recently, neuroimaging has been employed, and generally MRI is the method of choice to detect brain abnormalities, which can be detected in up to 50% of patients with focal epilepsy (Woermann & Vollmar, 2009).

Children

While this research project focuses on adults with epilepsy, misdiagnosis in adults can occur where childhood-onset of epilepsy goes unrecognised. Children are specifically vulnerable to misdiagnosis,

and adding to the perplexity of diagnosis, a 10-year large scale study of children with epilepsy found they had a higher incidence of non-epileptic than epileptic seizures (Bye, Kok, Ferenschildand, & Vles, 2000). However, Juvenile Myoclonic Epilepsy [JME], an idiopathic generalized epileptic syndrome with onset in childhood or adolescence may be widely underdiagnosed, and normal EEG readings have been found in these patients ranging from 6.3% to 38.9% (eg. Montalenti, Imperiale, Rovera, Bergamasco, & Benna, 2001). As one study highlighted, nearly 2 out of 3 children (57%) were incorrectly diagnosed with non-epileptic seizures when they had epilepsy (Parra et al., 1999). This is unacceptable as it is only just higher than chance levels, and such inaccuracy is not appropriate for the diagnosis of a common neurological disorder. In a study by Baise-Zung and colleagues, 54.3% of all males with epilepsy presented at least one normal EEG during follow up (Baise-Zung et al., 2006). Together, such evidence illustrates how the system for diagnosis has been wholly inadequate. As a consequence, it is no surprise that the recent clinical use of Video-EEG (V-EEG) telemetry monitoring for a prolonged period of time has increased accuracy for prior misdiagnosis of epilepsy in the last few years, and facilitated the identification of epileptic seizures where epilepsy has not previously been found (Engel, 2001; Kanner, 2008).

Interictal epileptiform discharges

Abnormal activity between seizures are known as interictal epileptiform discharges [IED's] and these can differentiate between either epileptiform or non-epileptiform activity (Noachtar & Remi, 2009). IED's are rarely, if ever, found in healthy individuals. For example, one study of 100 healthy volunteers found no IED's on investigation (Jabbari, Russo, & Russo, 2000). In children with epilepsy in remission, persistent IED's are associated with higher risk of seizure re-occurrence, however, persistent IEDs in adults are not yet fully understood (Noachtar & Remi, 2009).

IEDs and limbic seizures

Edward Bertram (2009) provides a hypothetical explanation for why IEDs at the seizure foci do not always transgress into a seizure. Seizures do not occur in isolated neurons, but as an assemblage of neurons which can be both local and remote across a circuit. The interactions within the circuit determine whether there will be a seizure or not. For example, absence seizures and limbic seizures depend on at least two components: the cortex supplying the excitatory drive, and the thalamic nuclei to organise this into an ictal discharge and for a seizure to occur. However, limbic seizures may involve more than two components (Avoli & Gloor, 1982). According to Bertram, this occurs because the threshold for the electrical current required to induce limbic seizures is significantly higher in the thalamus, and therefore multiple limbic sites need to be activated to drive the seizure (Bertram, Zhang, & Williamson, 2008). These sites include the amygdala, hippocampus, entorhinal cortex and

the midline thalamic nuclei, in which it is relatively easy to create limbic seizures in kindling models as they are associated with an increased excitability in the neurons (ibid.). What is interesting is that these regions can be either implicated in independently initiating a seizure, or can remotely drive another region to seizure activity by remote influence.

2.7 Classification

Epilepsy is not one single condition, but a range of syndromes encompassing about 30 epileptic syndromes and over 38 seizure types (Engel, 2001). Some researchers consider epilepsy as a continuum of symptoms representing an epilepsy spectrum disorder (Ryan et al., 2006). Epilepsy syndromes are classified according to the ILAE classification which is based on age, clinical semiology and electrophysiological findings (Sander, 2004). The ILAE provides a diagnostic manual of standardised definitions of epilepsy, and in 2009, proposed changes for classifying seizure types. The discussion and report of the full classification is beyond the scope of this thesis. However, generally, epileptic disorders have historically been divided into two dichotomous classifications: focal and generalised. A focal seizure does not mean the epileptogenic region is focal, but that it has a focal onset, and is considered to implicate a focal area in just one hemisphere of the brain. Focal epilepsy is very common and about 70% of all epileptic patients experience focal seizures ("The Psychiatry Research Trust - Epilepsy," 2011). A generalised seizure is considered to implicate both hemispheres of the brain. There are six types of generalised seizures; they are subdivided into tonic-clonic, absence, myoclonic, clonic, tonic, and atonic seizures (Berg et al., 2010). These seizures are differentiated by presenting as loss of consciousness, convulsions and muscle rigidity (tonic-clonic); brief loss of consciousness (absence); sporadic movements (myoclonic); repetitive movements (clonic); muscle rigidity (tonic); and loss of muscle tone (atonic) respectively. However, advanced neuroimaging studies have challenged this division and contributed to an interesting debate surrounding whether this distinction of epilepsy syndromes is accurate.

A specific illustration of this debate is TLE. TLE is defined as recurrent and unprovoked seizures originating from the medial or lateral temporal lobe. Misperception arises as temporal lobe seizures are not confined to the temporal lobe, but can spread to other anatomically connected brain regions outside the temporal lobe (Raj, Mueller, Young, Laxer, & Weiner, 2010). In addition, recent evidence suggests that those with TLE have lower connectivity to brain regions such as the medial prefrontal cortex (Frings, Schulze-Bonhage, Spreer, & Wagner, 2009). More surprising is that patients with TLE show memory deficits associated with functioning of the unaffected temporal lobe (Dupont et al., 2002). Researchers are currently trying to understand the network mechanisms underlying TLE, as it is clear from recent neuroimaging studies that such abnormalities are not confined to a single lobe or a

single hemisphere. This suggests that epileptic activity in focal epilepsy can cause widespread disruption across networks and hemispheres, which challenge the concept of ‘focal epilepsies’. Adding to this debate is further critical evidence which challenges the concept of ‘generalised’ epilepsy. Conclusions of a literature review of advanced neuroimaging of JME states that, rather than progressing across the whole cortex, it predominantly involves the frontal lobe (Anderson & Hamandi, 2011). Findings from this review have lead some researchers to call for the reclassification of JME, which is the most common generalised epilepsy in children, as a frontal thalamocortical network epilepsy (ibid., p.127). The outcome of similar future studies is likely to continue to challenge current classifications of epilepsy, and potentially provide a basis for further revision. These advances reposition certain epilepsy syndromes and are important for the investigation of autistic characteristics in epilepsy, as expectations that individuals with epilepsy have behaviour and cognition impairments exclusively related to the foci defined by their epilepsy syndrome may not be useful in terms of assessment of psychological functioning.

Reliability

Epileptologists presently have difficulties classifying seizures according to standardised classifications, and the reliability of ILAE epilepsy classification has been questioned. A study by Kellinghaus attempts to directly address the reliability of ILAE epilepsy classification (Kellinghaus et al., 2004). Kellinghaus and colleagues classified 185 epilepsy patients, and found that only four 4% of adults were diagnosed with a specific epilepsy syndrome of the ILAE classification. All other patients were in unspecific categories that provide incomplete and insufficient information for patient management, and for 15% of patients, it remained unclear whether their epilepsy was focal or generalised. Some patients could not be classified due to lack of EEG information, again suggesting an overreliance on a tool known for imperfect diagnostic accuracy. However, inter-rater agreement, the degree of agreement between the raters, was high. About one third of participants in this study had more than one type of seizure, and diagnosis of a single epilepsy type does not rule out the presence of a secondary unidentified seizure types after diagnosis.

2.7.1 Seizure Auras

This research focuses on ‘seizure auras’, which are classified as a ‘focal epilepsy’. Focal seizures, previously known as partial seizures, were subdivided into simple partial seizures (seizure auras without loss of consciousness), and complex partial seizures. However, in 2009, the ILAE recommended that the distinction between the different types of focal seizures (e.g. complex partial and simple partial) is eliminated (Berg et al., 2010, p.678). Although seizure aura is a focal epileptic seizure, the term ‘aura’ is endorsed by the ILAE (ibid., p.680). Seizure auras are usually but not

always discretely localised, with symptoms that are clinically relevant signs indicating the sites of origin or close proximity to regions from which they originate (Inoue et al., 2000, p.133). They disrupt normal brain functioning, and relate to the early phase of localised epileptic discharge within the brain, denoting the ictal onset of epilepsy. Auras occurs in approximately 80-90% of adults with temporal lobe seizures, and significantly more frequently in mesial than extra-mesial seizures (Fogarasi et al., 2007; Hoffmann, Elger, & Kleefuss-Lie, 2010). Mesial TLE (mTLE) is a common form of epilepsy denoted by hippocampal sclerosis [HS], the formation of scar tissue in the hippocampus, a region of the temporal lobe. Seizure auras are a stage of epilepsy which occur without loss of full consciousness, but awareness is lost as the seizure spreads to involve both temporal lobes (Nakken, Solaas, & Kjeldsen, 2009). Seizure auras present with sensory or autonomic symptoms such as somatosensory and sensory phenomena, disturbing all five senses (Kasper, Kasper, Pauli, & Stefan, 2010). Such phenomena can sometimes be referred to as hallucinations, which are defined as a sensory perception in the absence of adequate external stimulus (ibid., p.14). Auras can lead to experiences of being unable to use or comprehend language, déjà -vu, jamais-vu, fear, olfactory, gustatory and visual perceptual distortions of shape, size, distance of objects and people, and tunnel vision (ibid.). Autonomic phenomena can include changes in heart rate, rising epigastric sensation, and nausea. Seizure auras are common in those patients with less severe unilateral epilepsy with a slow onset, and surprisingly, they are more commonly associated with childhood than adulthood epilepsy onset (Inoue et al., 2000).

Prolonged auras that are not followed by a more severe epileptic event are termed 'isolated auras' as they occur as in isolation and remain as the only presentation of the epileptic seizure. Isolated auras have also been found to be more common in medial temporal lobe epilepsy [MTLE] (Janszky, Schulz, & Ebner, 2004). These auras are related to activity within the right hemisphere, in contrast to activity within the left hemisphere which evolves into a more rapid and severe epileptic event (ibid.). Although severely under-reported, many individuals can reliably describe the experience of their seizure auras. Research of seizure auras is primarily descriptive rather than informative, with the objective of distinguishing between phenomenon. While there has been an increase in research of seizure auras in more recent years, there is little research evidence of the daily effects of seizure auras, and their characteristics are still under debate. What is known is that seizure auras can be mild and non-convulsive, are associated with a variety of clinical manifestations. So far, research has not associated seizure auras with specific behavioural outcomes, or behaviour patterns. This is surprising given the seriousness and extent of their impact. Identifying and understanding any behaviour associated with seizure auras is essential, as this relationship is largely unconnected and incomplete, and as such, the effect of auras on daily life may be underestimated.

2.7.2 Network disease

More recently, epilepsy is being considered as a condition associated with abnormal functional networks, which brain-imaging evidence suggests are detectably different even when there is no epileptic activity (Zhang et al., 2011). Specifically in mTLE, it has been suggested that the neuro-physiological mechanisms of functional impairments may be related to a disorder of neural networks (Zhang et al., 2009). Epilepsy Research UK has recently stated that scientists now believe that epilepsy arises across networks of interconnected brain regions, and that the pattern of epilepsy depends upon a) the networks that are affected, b) the areas of the brain involved, and c) how the networks interact with each other (Epilepsy Research UK, 2011). At present, some researchers propose that some specific epilepsies such as TLE should be considered a ‘network disease’, defined by areas of decreased functional connectivity rather than origin of onset (Bettus et al., 2011; Grant, 2005).

2.7.3 Prognosis

The prognosis of epilepsy is defined as the chance of recovery or prediction of outcome, such as remission, recurring seizures, or chronic epilepsy. Extending the perspective of epilepsy as a neural network disease, Aslan and colleagues ask whether artificial neural network modelling could predict prognosis of epilepsy according to risk factors (Aslan, Bozdemir, Sahin, & Noyan Ogulata, 2010). The model revealed that the crucial risk factors for epilepsy prognosis were febrile convulsion (21.9%), kinship of parents (22.3%), history of epileptic relatives (21.6%) and history of head injury (18.6%); the researchers report a 91% correct prediction rate for prognosis. This model is useful as it highlights the genetic impact of epilepsy on recovery.

2.7.4 Prodromi

A prodrome is an early symptom indicating the onset of an epileptic seizure before the emergence of full symptoms. Promodal activity is rejected as a consideration of this thesis. As David Taylor states in his paper titled: ‘Whatever happened to the ‘epileptic prodrome?’, prodromes are not something that have been studied scientifically or mentioned commonly in the literature in relationship to epilepsy (Taylor, 2007, p.252). As such, prodromi are not a consideration of this research project.

2.8 Causes

Causes of epileptic seizures are termed:

Idiopathic, no identifiable cause;

Cryptogenic, a likely cause which has not been identified;

Symptomatic, a known cause.

Idiopathic seizures account for around 60% of all epilepsy cases (ERUK, 2011). There are numerous causes such as genetic influences, head trauma, toxins, medical disorders such as stroke, infections such as encephalitis, and prenatal injury. However, the most common known cause for epilepsy and seizures is birth trauma in humans, and febrile seizures in infancy have been linked to temporal lobe seizures in later life in animal studies (Dubé et al., 2010). Early postnatal testosterone has been identified as a factor which may increase the risk of seizures in males but not females in animal studies (Velisek, Veliskova, Giorgi, & Moshe, 2006). However, evidence for biological origins of seizure activity may not yet be fully identified or well-understood in humans with epilepsy.

2.8.1 Neurodevelopment

Childhood-onset of epilepsy has long been associated with severe neuro-developmental impact on brain structure, functional connectivity, and cognition. Frequent seizures in childhood may lead to irreversible connectivity changes in important neuronal pathways (Kellinghaus et al., 2004). Animal studies reveal that seizures result in reorganisation of synaptic networks (Holmes, 2002). Experimental studies during the developing animal brain suggest that if repeated seizures occur early in life, their effects can lead to long-lasting alterations and changes in network activity which may or may not lead to epilepsy in later life (Ben-Ari & Holmes, 2008). A recent animal study has demonstrated that both abnormal pre-frontal cortex [PFC] functioning and a thicker prelimbic PFC can result from early-life seizures (Kleen et al., 2011). Further, these brain structural abnormalities correlated with measures of impaired behavioural flexibility, which is mediated by the PFC. This implies that early-life seizure induced alterations in the PFC are likely to contribute to inflexible behaviour. The researchers suggest that long-term alterations in neuro-transmission from early seizures may provide a mechanism for the co-occurrence of autism and epilepsy. Further, they state that their findings are consistent with abnormal and increased brain growth found in autism. However, despite these interesting findings, early-life seizures cannot yet provide a model of autism, as their impact upon socialisation and language deficits have yet to be determined. Evidence for the neuro-developmental hypothesis originates from brain volumetric studies which show that early onset TLE has a negative effect on extratemporal cortical development (Kaaden & Helmstaedter, 2009). As chronic epilepsy patients often perform worse in cognitive assessments, Helmstaedter and Elger attempt to directly address the question of whether chronic TLE is a progressive disease, or whether there is a neuro-developmental hindrance (Helmstaedter & Elger, 2009). Their study indicates a developmental hindrance which suggests that TLE should not be regarded as a progressive disease, but that at its origin, epilepsy interferes with brain maturation and cognitive development (ibid.).

A fundamentally different line of enquiry has led to the possibility of a neuro-developmental cause to onset of epilepsy in TLE. This is of immense interest, as the majority of patients have no identifiable cause for their epilepsy. In recent years, studies have identified that limbic cortical malformations are a common finding in patients with MTLE as they undergo surgery. This suggests that maldevelopment in the cortex may lead to persistent changes in network properties within the brain, resulting in TLE. A recent study by Voets and colleagues (2011) explored the relationship of hippocampal malrotation, which is rarely found in individuals without seizures, and cortical abnormalities with TLE (Voets, Bernhardt, Kim, Yoon, & Bernasconi, 2011). The researchers found that TLE was associated with increased folding of the temporal limbic and neocortex, which the researchers' state is suggestive of a common neuro-developmental phenotype with maldevelopment of the temporal lobes, as an important factor in the development of TLE. Subsequent research has found that specific aspects of cerebellar atrophy may also be associated with neuro-developmental features of TLE (Oyegbile et al., 2011). Interestingly, one study has identified a non-significant but extremely high rate [85.7%] of under 5's with TLE to have cortical developmental abnormalities (Terra-Bustamante et al., 2005). According to Voets and colleagues, cortical developmental abnormalities may indicate a developmental basis for TLE, suggesting that TLE in children under 5's may indicate a common neuro-developmental phenotype.

2.9 Consequences

Manifestations of epilepsy include severe psychological and cognitive impairment, and these consequences of epilepsy are often as serious as having the disorder itself (Baker et al., 2004). Much debate has centred on whether seizures are a cause or the result of brain damage. It is now recognised that both are true. Seizures can last for hours and cause brain injury, regardless of whether they are focal or generalised (Holmes, 2002). Individuals with continual seizures are 3 times more likely to be clinically depressed, twice as likely to have anxiety, more likely to feel stigmatised and experience psychological distress (Buck, Smith, Appleton, Baker, & Jacoby, 2007). Children with epilepsy are up to 4.7 times more likely to have behaviour problems than their peers (Schachter, Holmes, & Kasteleijn-Nolst Trenite, 2008, p.456).

2.10 Anti-Epilepsy Drugs (AEDs)

AEDs are known to achieve full seizure control in up to 70% of individuals with epilepsy (Elger & Schmidt, 2008). However, all main AEDs are reported to be associated with cognitive side effects, can be potentially life-threatening, and the effects of AEDs on the unborn child are well reported (Cross, 2010; Perucca, Carter, Vahle, & Gilliam, 2009). Patients taking multiple AEDs reported significantly higher levels of adverse effects and worse seizure control (Moran et al., 2004). While a

full discussion of the cognitive effects of AEDs are beyond the scope of this thesis, multiple reviews and studies suggest that AED usage correlates with impairments on tests of memory, attention / vigilance, visuomotor tests, psychomotor speed, and reaction time (Aldenkamp, 2001; Hessen, Lossius, Reinvang, & Gjerstad, 2006). AEDs are related to a decline in performance IQ, concentration, memory, visuomotor functions and mental speed, and generate anxiety, aggression, fatigue, and depression; valproic acid can impair complex decision making (Cavanna, 2010). AEDs are also widely administered to individuals with ASD (Di Martino & Tuchman, 2001). During a review of 95 articles on the current use of AEDs for the treatment of ASD, Di Martino and Tuchman (2001) found that AEDs were a significant factor for improving deficits in two of the three core characteristics of autism: communication and socialisation. This supports previous anecdotal evidence which suggests that AEDs lead to improvements in communication and behaviour in those with ASD and epileptic discharges (ibid.). However, their evidence is based on case reports rather than controlled clinical trials, and they note that placebo-controlled, double-blind controlled studies of AEDs are clearly needed. The difference between uncontrolled and untreated epilepsy, is that adults with uncontrolled epilepsy are taking ineffective AEDs, while untreated adults are not taking AEDs.

Summary

Epilepsy is a severe and complex neural network disorder characterised by recurrent seizures. Notably, epilepsy is poorly understood, difficult to diagnosis, and recent evidence is currently challenging the standard classifications of epilepsy. Misdiagnosis and under-diagnosis have been highlighted by researchers, and careful consideration must be given to characterising specific patterns of cognition and behaviour which define epilepsy and epilepsy syndromes. It can be argued that while epilepsy can interfere with brain maturation and impair functional connectivity, a common neuro-developmental phenotype may also result in the development of temporal lobe epilepsy. It remains to identify which specific behaviours and cognitive abilities characterise epilepsy, specifically TLE and seizure auras, and relating theoretical understanding in such a manner that these characteristics can be easily understood.

Chapter 3

Autism Spectrum Disorders

“*I love mankind ... it's people I can't (under)stand*”

*Adapted from a quote by
Charles M. Schulz*

3.1 Origins of Identification

The term Autism from ‘autos,’ meaning self, is aptly named, implying isolation, and a solitary level of existence, in which those with autism are excluded from the shared social understandings of the world. In comparison to epilepsy, autism disorders are a relatively recent clinical addition. Autism was first identified by Leo Kanner and Hans Asperger who each independently published papers within months of each other, and whose original observations founded the origins for identification of autism (Gillberg, 2002).

3.2 Definition and Diagnostic Criteria

There is not one single diagnosis of autism, but a spectrum of disorders commonly termed as autistic spectrum disorders [ASD] (Tuchman & Rapin, 2002). ASDs are a severe developmental disorder, diagnostically featured by the presence of “markedly abnormal or impaired development in social interaction and communication, and markedly restricted repetitive repertoire of activity and interests”, by the American Psychiatric Association’s Diagnostic and Statistical Manual, DSM-IV-TR (2000, p.70), see Table 3.1. Notably, social interaction impairment is gross and sustained. Abnormal functioning or a delay in social interaction, communication, and imagination, referred to as a triad of impairments, must be evident before 3 years of age. Onset after 3 years is defined as Autistic Regression [AR]. A diagnosis of Asperger’s Syndrome [AS] referred to in the DSM-IV-TR as Asperger’s Disorder is characterised by a lack of delay in language acquisition, defined by communication through the use of single words by 2 years, and spontaneous phrases by 3 years, DSM-IV-TR (APA, 2000, p.78 & p.80).

There is no medical test for ASD, and diagnosis involves gold standard diagnostic assessments, the most accurate diagnostic tests available, such as the Autism Diagnostic Observation Schedule which diagnoses autism and pervasive developmental disorders, and the Autism Diagnostic Inventory-Revised which diagnoses autism and distinguishes it from other non-pervasive developmental disorders (Berument, Rutter, Lord, Pickles, & Bailey, 1999; Lord et al., 1989). However according to Winner, standardised tests are limited and may not portray an accurate picture of the difficulties in on-going communicative interactions (Winner, 2002).

Table 3.1: ASD Diagnostic Criteria

Autistic Disorder [AD]	Asperger's Syndrome [AS]
<p>A. (1) qualitative impairment in social interaction. (2) qualitative impairments in communication. (3) restricted repetitive and stereotyped patterns of behaviour, interests and activities.</p> <p>B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, (3) symbolic or imaginative play.</p> <p>C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder</p> <p><i>A total of six items from the social, communication and behavioural criteria are required. Delay in at least one of these domains must occur before age 3 years.</i></p>	<p>A. Qualitative impairment in social interaction.</p> <p>B. Restricted repetitive and stereotyped patterns of behaviour, interests and activities.</p> <p>C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.</p> <p>D. There is no clinically significant general delay in language.</p> <p>E. There is no clinically significant delay in cognitive development, or in the development of age-appropriate self-help skills, adaptive behaviour and curiosity of about the environment of childhood.</p> <p><i>Criteria are not met for other PPD's or Schizophrenia.</i></p>

(DSM-IV-TR, 4th edition, 2000, p.75 & p.84)

Asperger's Syndrome

Asperger's Syndrome was first defined by Asperger and re-examined by Lorna Wing (1981) who outlined the clinical features of AS from her own observations. Notably, Wing modified two of Aspergers' original points from his observations. Firstly, Wing stated that those with AS do not usually talk before they can walk, noting that speech was impoverished. Secondly, she highlighted that their creativity may be confined solely to a narrow area of interest. These precise modifications led to the formulation of the first set of diagnostic criteria by Gillberg (Gillberg & Gillberg, 1989). Asperger's Syndrome differentiates from AD not only through language, but additionally social interaction patterns in AD are marked by self-isolation or rigid social approaches, whereas AS

individuals have motivation for approaching others, although this can be eccentric, one-sided, verbose, and insensitive (APA, 2000, p.84).

High-functioning Autism

The term high-functioning autism [HFA] has been applied to autistic individuals with average or above average intellectual abilities. Empirical research has established that in addition to their atypical language development, those with HFA perform worse on theory of mind and verbal memory tasks, while those with AS have normal language development but have difficulties with their social use of language (Ozonoff, Rogers, & Pennington, 1991a; Speirs, Yelland, Rinehart, & Tonge, 2011). However, further research needs to establish the extent to which HFA and AS are distinguishable.

Autistic Regression

Autistic regression is marked by a rapid and pronounced deterioration in core symptoms of ASD, with specific regression in communication and social behaviour (Matson & Kozlowski, 2010). Of interest, around one third of parents of autistic children claim their child regressed between 18-24 months old after a period of normal development. Parental detection has been consistently shown to be sensitive and a specific indicator for identifying ASD (Werner, Dawson, Munson, & Osterling, 2005). Further, no difference was found between early and late onset of symptoms (ibid.). On this basis, such claims should be considered seriously. The prevalence, causes and theories of ASD are outlined below, and characteristics common to ASD and epilepsy are discussed in Chapter 4.

3.3 Prevalence

Early reports estimated the prevalence of ASD at 4–5 per 10,000 births (Fombonne, 2003). Although rates had been considered to reach a plateau around 1996, rates have recently increased to 91 per 10,000 births, nearly 1 in 100 individuals in the UK (Brugha et al., 2007). Currently, the average male to female ratio [M:F] is 4.5:1 (Murphy, Beecham, Craig, & Ecker, 2011).

3.4 Cause

Autistic spectrum disorders are a condition with multiple causes with biological origins which fall in two basic categories: genetic or non-genetic. The high co-morbidity of epilepsy in autism were early indicators that ASDs are a neurological condition rather than a result of poor parenting, and that both conditions share common neuropathological features supported by neuroimaging studies (Peake et al., 2006). Specific genetic causes have been highlighted in section 4.1.1 where syndromes are related to both epilepsy and autism. The presence of syndromes in the co-morbidity reveals the strong genetic

basis of ASD which is usually accepted as a primary causative agent between epilepsy and autism (ibid.). However no single gene has been linked specifically to autism, and only about 10-20% of autism cases have been traceable to an underlying genetic cause (Beaudet, 2007). More to the point, outside these underlying genetic causes for ASD syndromes, there is no evidence to suggest that epilepsy is causal.

Early biological factors contribute to alteration of brain functioning causing developmental cognitive abnormalities which characterise autistic traits. Although no single biological basis for autism has been found, one specific finding has been demonstrated by positive correlations of foetal testosterone levels and autistic traits (Auyeung et al., 2009). The high-testosterone prenatal environment implicated in the etiology of ASDs supports a prominent theory of ASD (see 3.4). The implications of genetic influences and early testosterone are supported in a study by Brosnan and Walker (2009). Brosnan and Walker demonstrated that fathers of children with ASD do not consistently show a preference for attraction to females with lower-than-average Waist-hip ratio, which indicates the woman's lower circulating testosterone level. The genetic implication of this is that offspring from fathers of children with ASD and their female partners are likely to have a higher-than-average prenatal testosterone exposure.

Key to understanding causes of autism, highlighted by Beaudet (2007), are studies which demonstrate why autism is heritable, but not an inherited condition. High heritability has been consistently shown largely due to high concordance in monozygotic twins and low concordance in dizygous twins. However, only 10-20% of autism cases are traceable to an underlying genetic cause (ibid.). Mostly, these are new genetic mutations that are not present in or transmitted by parents of children with ASD. Therefore while genetic causes of autism have high heritability and therefore cause the autism, these genetic mutations are not inherited. Note that the genetic heritability does not explain the M:F ratio, an important point which should not be overlooked, since the mutations affect both sexes equally (ibid.). Plausible explanations for the M:F ratio in ASD and the broader autism phenotype [BAP] have not yet been established through genetics. Such a genetic link for autism is further problematic, specifically as it fails to explain the dramatic increase in prevalence rates. Although heritable, 80-90% of cases are idiopathic and multiple environmental factors have been highlighted, such as an early environmental insult (Beaudet, 2007). Environmental insults of concern currently under investigation include exposure to neuro-developmental toxicants such as pesticides, metals, persistent pollutants with known or suspected neuro-developmental or immunologic toxicity; medication, infections and other treatments; and insults caused by conditions at birth such as birth procedures (Irva et al., 2006). For example, Lorna Wing found that nearly half of the 34 cases which

she had personally examined and diagnosed had a history of pre-, peri- or post-natal conditions or birth trauma which can cause cerebral damage (Wing, 1981). Unfortunately, there has been little progress in a reduction of these factors.

A more recent proposal is that autism is a neurobiological disorder caused by abnormal neural connectivity (discussed in 3.10). Some researchers go further, and suggest that autism is marked by and caused by specifically under-functioning integrative circuitry (Just, Cherkassky, Keller, & Minshew, 2004). What is commonly agreed is that autism is a behaviourally-defined life-long neuro-developmental disorder which is the endpoint of several different organic aetiologies. It remains to be seen what further identified causes will be associated with ASD; however, it is likely that a genetic predisposition and multiple environmental factors contribute to the aetiology.

3.5 Autism as a trait condition

It is generally accepted that the BAP found in relatives of those with ASD is strong evidence for ASD as a trait condition (Scheeren & Stauder, 2008). These autistic traits are found in the general population as a continuum in which the boundaries are unclear. However, as Happé points out, there is no evidence of a bimodal distribution separating clinical and non-clinical deficits within the triad (Happé, Ronald, & Plomin, 2006). This is fundamentally important for understanding ASD, as the current spectrum is extremely broad. Behavioural and psychometric tests commonly demonstrate that parents of ASD children score higher for autistic characteristics. However, these parents may not be naïve to the characteristics being sought for, and may have been informed about autistic traits during the diagnostic procedure of their child. Scheeren and Stauder (2008) examined whether the BAP was myth or reality, however the parents of children with ASD showed no more autistic traits on the AQ than control parents in their study. Differences were found in empirical measures demonstrating slower reaction time, particularly on the eye gaze task. However, this was only demonstrated by fathers, and slow reaction time could be accounted for by the stress of being a parent of an ASD child. Other empirical studies claim compelling evidence for autistic characteristics in BAP (eg. Dalton, Nacewicz, Alexander, & Davidson, 2007). While further research is needed to demonstrate significant functional differences in the BAP, a neuro-physiological correlate for familial susceptibility has been demonstrated through fMRI (eg. Belmonte, Gomot, & Baron-Cohen, 2010). But exclusive to ASD are the significant anatomical and functional differences which are found even in young children. What is required then, are assessments with cut-off scores congruous with empirical research of brain structural and functional abnormalities in ASD not found in the general population or the non-clinical BAP. For example, one key finding is of hippocampal-shape deformations in children with ASD who

exhibit deficits on neuropsychologic tests of medial temporal lobe functioning (Dager et al., 2007). This specific hippocampal shape can distinguish children with ASD from children without ASD. More to the point, it specifically distinguished children with ASD from those with pervasive developmental disorder, not-otherwise specified [PDD-NOS]. This pattern was more accentuated in the more severe children with ASD, suggesting the possibility of a strong relationship. And of particular note is that this pattern of hippocampal-shape deformation has only been observed otherwise in adults with MTLE. While this does not imply causality, it has recently been suggested that hippocampal shape formation in MTLE, may be a neuro-developmental phenotype (2.8.1). Importantly, such a distinguishing feature questions the recent inclusion of PDD-NOS under the amended ASD category proposed for DSM-5. Although a BAP has been identified, no evidence has been found in a large-scale study for the sex difference in the prevalence of ASD among male and female relatives, therefore importantly, this phenotype fails to explain the M:F ratio (Goin-Kochel, Abbacchi, & Constantino, 2007). So far, this remains unexplained. Additionally, few studies have investigated motor dysfunction in the BAP. Although not a core characteristic, they are common to ASD. For example, 90% of the 34 cases of children with AS personally examined by Lorna Wing presented poor motor skills (Wing, 1981). Although evidence suggests ASD are a trait condition, they are still a heterogeneous group of conditions with multiple aetiologies, and pathophysiologies.

3.6 Adults with autism spectrum disorders

Understandably, research has focused on understanding the neuro-developmental basis for autism, rather than autism as a life-long condition. Longitudinal studies of adults with ASD are lacking, and relatively little is known about the biology of adults with ASD. However, some studies have highlighted age-related changes such as improvements in executive functioning, repetitive behaviour and eye gaze detection (Hughes, 2009). Murphy and colleagues highlight differences of brain maturation across the lifespan of the ASD adult (Murphy et al., 2011). Despite differences, the neuropsychological profiles of AS adults remain into adulthood, and AS adults continue to score high for autistic traits. More significantly, adults with AS continue to have impaired social cognition (Lehnhardt et al., 2011). The National Institute of Clinical Excellence (NICE) are presently developing guidelines for diagnosis and management of ASD in adults, due to be published in 2012.

3.7 Sex differences in ASD

Little research has compared males to females with ASD, however a recent study by Lai and colleagues found that females presented more sensory but less socio-communication symptoms, and scored higher for autistic traits in adulthood than males (Lai et al., 2011). Overall, such studies are lacking. Gillberg (2002) states that it is quite conceivable that current prevalence rates for females

could be underestimated. It has been suggested that screening tools may be poorly adapted for identifying ASD in females as many tests have been developed around characteristics of ASD from a male-biased research field. According to Richard Mills of the National Autistic Society, diagnostic stages differ according to gender, boys are more likely to be diagnosed at 5-7 years of age, but girls are usually adolescent or older (Rose & Carlyle, 2010). Murphy and colleagues found that females have significantly more brain abnormalities than males in order to express the same severity of autistic symptoms suggesting that the female brain offers some protection in the regions implicated (Murphy et al., 2011). Tsakanikos and colleagues state that sex difference in clinical symptoms could account for prevalence differences (Tsakanikos, Underwood, Kravariti, Bouras, & McCarthy, 2011). To this aim, Kopp and Gillberg developed an extension of the Autism Spectrum Screening Questionnaire for the female phenotype of ASD and initial findings provide some insight into different behaviours typical of girls (Kopp & Gillberg, 2011).

3.8 Theories of Autism Spectrum Disorders

This section discusses and evaluates the most predominant theories of ASD: Executive Dysfunction Theory, Theory of Mind and Weak Central Coherence Theory.

3.8.1 Executive Dysfunction Theory

The executive dysfunction theory [EDT] proposes that executive functioning abilities are the main deficit in ASD. Executive functioning is a term used to describe a set of cognitive abilities that control and regulate processes such as planning, organisation, problem-solving, working memory, mental flexibility, social functioning, impulse control, self-monitoring, and the monitoring of action. Executive functioning deficits were originally identified in HFA by Sally Ozonoff, Bruce Pennington and Sally Rogers (1991b), and in 1997 James Russell drew together the evidence for this theory, arguing that a deficit of executive function systems are central to understanding autism (Russell, 1997). Together, these researchers focused on specific difficulties associated with autism which suggested a dysfunction of a specific area of the brain, the pre-frontal cortex. Executive functioning depends upon intact frontal lobes functioning, especially the prefrontal cortex, and predominantly underlies social impairments and rigid and repetitive behaviours in ASD.

Social communication requires complex planning abilities, organisation of language, along with continual adjustment and self-control. In addition, those with ASD can be impulsive, and often focus on one narrow interest, or engage in stereotypic behaviours. Given the high presentation of such behaviours, many researchers conclude that this theory can explain social and non-social core characteristics in ASD. Notably, research by Ozonoff and Jensen (1999) strongly suggested that a

specific pattern of executive dysfunction can distinguish ASD from other developmental disorders. Of the 6 domains of executive functioning, cognitive flexibility emerged as the key domain related to repetitive behaviour. However, those with ASD do not always fail on tasks assessing cognitive flexibility, and studies yield inconsistent findings (Van Eylen et al., 2011). More to the point, there has been little consensus about what specific behaviours are common to ASD. This has been confounded by evidence of age-related differences of rigid behaviours in ASD (Esbensen, Seltzer, & Lam, 2009). Investigating such inconsistencies precisely, Van Eylen and colleagues confirmed that those with ASD have impaired cognitive flexibility, and performance is influenced by low explicit task instructions and the high disengagement needed to perform the cognitive switch (Van Eylen et al., 2011).

According to EDT, rigid and repetitive behaviours are assumed to be a characteristic with different domains underpinned by a unifying theoretical explanation. Assessments include categories from several domains as it is extremely useful for diagnosis, especially since no single repetitive behaviour is specific to ASD. However, from the perspective of research investigating theoretical underpinnings, the range of rigid and repetitive behaviours is arguably too broad. For example, stereotypy, the presentation of atypical motor automatisms, is related to the 'ictal' stage of epilepsy which is the primary co-morbid condition in ASD. Sameness behaviours may be a compensatory strategy for atypical memory processes. Self-injurious behaviour may be a response to frustrations born from factors within the environment, such as social difficulties. Consideration must be given as to whether these subscales require underlying explanations at differing levels. Researchers may benefit further from seeking out the hub of each difficulty as a separate entity, for example cognitive inflexibility has been strongly associated with EDT, but EDT cannot account for self-injurious behaviours, even from a social cognitive perspective. Research has only established strong factors for a few individual subscales, but the assumption that they represent a single underlying deficit could thwart attempts to understand why this pattern of behaviour exists. Given the high co-morbidity of epilepsy, such discrimination may yet yield bimodal distribution of data elusive to the BAP continuum.

3.8.2 Theory of Mind

One influential theory of autism is Theory of Mind [ToM], the ability to identify and attribute the mental states of others that are different from one's own, helping to form typical assumptions about others. Originally proposed by Baron-Cohen, Leslie and Frith (1985), ToM proposes that individuals with ASD have a diminished ability to understand the beliefs, intentions, thoughts and emotions of others, and this ability is considered to underpin social cognition. Those with ASD fail to use such assumptions, albeit correct or incorrect, to their own advantage in the social arena. An early study

suggested that ToM is not a universal deficit of ASD, but is impaired in varying degrees (Ozonoff et al., 1991a). The strong relationship between ToM and verbal mental age suggests that development of ToM is delayed in ASD (Happé, 1995). Although those with AS may have a theory of mind deficit, they can be successful with simple tasks about the beliefs of others, probably by employing conscious, effortful strategies, rather than through automatic processes. ToM provides an excellent understanding of social cognitive differences in ASD and has led to great progress in understanding human social cognition. However, ToM only partially addresses the complexity of the social difficulties faced by those with ASD. ToM assessed through eye-gaze tasks fail to explain impaired eye-gaze can arise in the newborn, while ToM develops at a much later age around, mostly likely after 3 years of age (Wellman, Cross, & Watson, 2001). Not only is it difficult to empirically demonstrate that a typical week-old infant should have ToM, but also difficult to demonstrate that any toddler under 3 years has ToM. Therefore robust findings from eye-gaze tasks may be related to developmental failure after the diagnostic period of ASD. Therefore different explanations are required for impaired eye-gaze in the newborn infant. For adults, what is ideally required in assessing abilities such as eye contact engagement is inclusion of the inseparable social expectations within the context that underlies the social interaction. Nevertheless, this theory is well-supported by fMRI evidence that has identified low functional connectivity within the ToM network in ASD (Mason, Williams, Kana, Minshew, & Just, 2008). More recently, this level of connectivity has been related to reciprocal social impairment in ASD (Consortium, Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011).

Theory of mind has been criticised for its all-or-nothing approach, test-retest reliability, its inability to account for non-social characteristics, and fundamentally, individuals with AS have performed well on high level ToM tasks despite ‘pronounced’ social disabilities (Klin, 2000). This missing relationship led Klin to include some valuable new measures, such as spontaneous search for social meaning in stimuli, adding insight to current research methods. ToM needs to reduce the disparity between the theoretical model and social cognitive difficulties in the naturalistic environment, and tasks with high accuracy and specificity for ASD are needed to bridge this gap to fully understand how the self interacts and responds to the social environment. Even if the current studies designed to assess ToM are limited by their very nature, difficulties with social perspective-taking is a core characteristic which should be the focus for any theory of ASD.

3.8.3 Weak Central Coherence Theory

Originally posited by Frith, the Weak Central Coherence theory [WCC] proposes that individuals with ASD fail to integrate the component parts of information into a globally integrated ‘Central Coherent’ whole (Frith, 1989). Although some authors have attempted to bind ToM and WCC theory together

with the perspective of highlighting an overlap, WCC differs from ToM by its explanation of the non-social characteristics of ASD, such as attention-to-detail. This theory accounts for a weak or absent ability for global integration to combine information for other possible meanings at a 'higher-level'. This theory proposes that those with ASD have an 'imbalance' and therefore the theory accounts for some of the patterns of strengths found in ASD. Therefore WCC theory is also supported by tasks assessing these strengths.

In 1983, Shah and Frith presented findings of a superior local processing ability in locating a small target shape embedded within a larger shape in ASD, employing the Children's Embedded Figures Test [CEFT] (Shah & Frith, 1983). To relate such findings to the theoretical understanding of WCC, Happé conducted an empirical study and demonstrated that those with ASD did not succumb to visual illusions, and this was least likely for 2-D rather than 3-D pictures (Happé, 1996). Accepting this as evidence of failure to integrate information pieces into a coherent whole, Happé argues from the perspective of task success rather than task failure for this cognitive bias. Current evidence suggests that this superior ability is unique to ASD. According to a review by Plaisted and colleagues, local processing was found to be enhanced in ASD, but not at the expense of global processing (Plaisted, Saksida, & Weisblatt, 2003). In support of the BAP, this ability was found in fathers of children with ASD who demonstrate a significant advantage on EFT.

WCC is hypothesised to provide an explanation for enhanced attention-to-detail abilities, a subscale of the AQ, and performance of enhanced attention-to-detail is considered to be a criterion for systemizing (Baron-Cohen, 2002). More recently, the WCC theory has been extended to explain higher level conceptual abilities such as language impairment. Inconsistent evidence and lack of a superiority effect have been found in some studies (eg. Mottron, Burack, Stauder, & Robaey, 1999). This suggests that either this ability is found to varying degrees, is unstable, or that this is an incomplete theory. However, it fails to successfully integrate social responsiveness into the theory, which is core to identifying ASD.

3.9 Review of theories

It is important to acknowledge that no theory can fully account for the triad of impairments, and these are not easily integrated into any single unified theoretical concept. Theoretical understandings fail to fully integrate with autism as a consequence of multiple biological systems. Theories of autism have been criticised for their lack of integration as the autistic traits only partially correlate, and encompass a very wide spectrum. Further, those with ASD face other difficulties such as motor coordination that

are not easily explained by any single theory. Neither are these autistic impairments confined solely to those with ASD, they overlap with other neurological conditions and mild non-clinical traits are found in the general population. According to Rajendran and Mitchell (2007), these theories do not take a developmental approach but account for a static style of cognitive impairment. This is surprising, given that over one third of those with ASD have a diagnosis of epilepsy, arguably the most dynamic neurological condition. Overall, the relationship of these traits to the onset and recovery of epilepsy as a specific significant factor is largely unexplored.

Lastly, there is a failure to integrate understandings from physiology, biology, genetics, and anatomy, multiple environmental factors into a coherent unification of ASD and its phenotype. However, even the most incomplete theory is beneficial, as these theories increase the understanding of ASD.

3.10 Functional Connectivity

The significant finding of underconnectivity in the brain of those with ASD was introduced by Hughes and Melyn, which was deduced from the finding that while 46% of children with ASD had seizures, a further 20% showed epileptiform discharges (Hughes, 2007). Such epileptiform discharges are rare in typical children, but of great significance is that these discharges occurred without any observed seizure activity. As epileptiform discharges are characteristically focal, the researchers proposed that lack of seizures from the foci strongly indicates underconnectivity, since underconnectivity explains lack of seizure spread, which would otherwise normally arise from the discharge. Hughes and Melyn were not the first to identify a high rate of abnormal EEG discharges, but were the first to provide an explanation that abnormal neural connectivity was due to underconnectivity. Subsequent multiple fMRI studies have strongly supported these initial findings. Although epileptiform discharges are characteristic of epilepsy, the significance of them in ASD still remains uncertain. Note though, Fisher and Engel (2010) state that IEDs are really fragments of seizures which affect cognition and behaviour (Fisher & Engel, 2010). Landau Kleffner Syndrome [LKS] is a good model of the epilepsy-autism co-morbidity, and importantly, demonstrates the behavioural and cognitive consequences of epileptiform discharges in children who have no observable seizures (Besag, Ahmed, Martinez, Yee, & Cahill, 2008).

Why functional connectivity is important to understanding ASD is explained in the work of Belmonte and colleagues, who integrate the triad of impairments and specific neuronal connectivity patterns (Belmonte et al., 2004). They conclude that such network connectivity patterns on brain activation are consistent not only with the triad of impairments, but also with impaired motor coordination,

perceptual abnormalities, and high co-morbidity of epilepsy. More precisely, this underconnectivity in the autistic brain is characterised by corresponding high local connectivity and low long-range connectivity. Unsurprisingly, they propose that it may account for perceptual differences relating to the WCC theory, such as atypical visual motion coherence and auditory filters (Milne et al., 2002; Plaisted et al., 2003). Accordingly, abnormal neural connectivity is an explanatory framework to unify evidence from genetic and neuropathological findings with neuroanatomy, neurophysiology, behaviour, and theory. Such a framework provides an extensive understanding of mechanisms underlying ASD. What remains to be identified is whether this explanation underpins the remaining non-social autistic traits such as repetitive behaviours. In a review of this explanatory framework, Levy additionally proposes that this may indicate a ‘developmental’ failure of neural connectivity (Levy, 2007). An interesting enquiry would be whether such functional connectivity is genuinely developmental, and how this relates to resolution of early-onset AR. What is important is that such coherence at this level of analysis represents a significant step forward, and may be useful in the future for integrating theoretical approaches to ASD.

Summary

Autism is a life-long developmental disorder, and the cause is mostly unknown. Several theories of ASD have been evaluated; however there is no single theory which successfully explains the specific pattern of cognition and behaviour in ASD. However, each theory attempts to address one or several domains and is robustly supported by multiple kinds of evidence, leading to increasing understanding of ASD in recent years. Most theories fail to account for neurobiological or physiological factors; however, underconnectivity provides a more comprehensive explanatory framework for understanding the wide range of profound differences of autism.

Chapter 4

Autism and Epilepsy:

A well-defined or uncomfortable co-morbidity?

Traditionally, autism falls under the domain of psychiatrists and behavioural specialists, while epilepsy falls under the domain of neurologists and epileptologists.

“Those fields have been divided for over 50 years and are only now coming together again in terms of diagnosis and treatment strategies.”

*Dr. Jay Salpekar (2011)
George Washington University*

This chapter evaluates the co-morbidity of autism and epilepsy, with a view to establishing whether this is a well-defined co-morbidity. Co-morbidity is defined as the concurrent presence of two or more medically diagnosed diseases in the same individual. Other co-morbid conditions are not a focus of this research.

4.1 Co-morbidity

One of the first children ever diagnosed by Kanner in 1943 with the term early infantile autism, had epilepsy. The high rate of epilepsy in ASD was an early indicator that autism was a neurobiological disorder. However, since these early findings, the co-morbidity has largely been ignored, and its relevance is still extensively debated.

4.1.1 Prevalence of Epilepsy in ASD

In the general population, a prevalence of 0.71% of epilepsy is found (see 2.3). The prevalence rates of epilepsy in those with a diagnosed ASD range from 13%-46% (Canitano, Luchett, & Zappella,

2005; Hughes & Melyn, 2005; Gabis et al., 2005). This compares with a 3-27% epilepsy rate in other pervasive developmental disorders (Miyajima et al., 2011). The prevalence rates are considered to be inflated where syndromes such as Fragile X or Tuberous Sclerosis Complex are included in the sample, since these syndromes are already associated with both disorders (Spence & Schneider, 2009). According to Nomura and colleagues, epilepsy in ASD is not the secondary manifestation, but denotes one of the symptoms that contribute towards a diagnosis of autism (Nomura, Nagao, Kimura, Hachimori, & Segawa, 2010). However, many researchers criticise this co-morbidity by stating that autism is part of a broader genetic phenotype which affects family members, while epilepsy is not part of the broader phenotype in autism (Mouridsen, Rich, & Isager, 2008). Most cases of epilepsy are idiopathic in which there is no known heritability; even so, a high rate of epilepsy has also been found in the broader spectrum of children with autism (Tuchman & Rapin, 2002). All seizure types have been recorded in those with ASD, however focal seizures are the most common seizure type (Peake et al., 2006). Recent research of 150 individuals with ASD has identified that while the presence of epilepsy in ASD was not associated with an increased risk of epilepsy in their relatives, the presence of epilepsy was associated with the presence of the broader autism phenotype in relatives (Bolton et al., 2011). Even so, little research has investigated autistic traits and characteristics in adults with epilepsy, or their relatives.

4.1.2 Prevalence of ASD in Epilepsy

Prevalence rates for the diagnostic criteria of an ASD in individuals with epilepsy are severely lacking. However, under-diagnosis is illustrated by Clarke in an unselected sample of children with epilepsy using the *Autism Screening Questionnaire*, in which 32% were found to be at risk of ASDs, with the majority of children being previously under-diagnosed (Clarke et al., 2005). The literature review examining ASD in children undergoing surgery for epilepsy reveals a wide range of prevalence ranging from 19% to 38% (eg. Taylor, Neville, & Cross, 1999; McLellan et al., 2005). This is higher than for the general UK population. In a retrospective study of patients with epilepsy and ASD, ASD was detected *after* epilepsy onset for 47% of the patients, and some of these cases had been overlooked for more than five years (Matsuo, Maeda, Sasaki, Ishii, & Hamasaki, 2010). Matsuo and colleagues state that HFA or AS is easily missed in epilepsy clinics, and state that it is important to suspect ASD in every patient with epilepsy (Matsuo et al., 2010). Further research is needed to establish the accuracy of this co-morbidity, and identify factors that implicate onset of ASD with the onset of epilepsy. While it is unclear if ASD are under-diagnosed in adults with epilepsy, evidence suggests that ASD are routinely suspected to be under-diagnosed in children with epilepsy (Clarke et al., 2005; Saemundsen et al., 2007; Steffenburg et al., 2003). Under-diagnosis has also been uncovered during research of children with seizure onset in the first year of life where it was found that 32% of children should have a diagnosis of ASD, yet less than one third of these had been

diagnosed (Saemundsen, et al., 2007). Steffenburg and colleagues identified 37% of ASD and Learning Disability [LD] in children with epilepsy, and suggested that autistic regression in these children had previously been misinterpreted as epileptic behaviour (Steffenburg, et al., 2003). Steffenburg suggested that previous studies may have failed to uncover such a high rate of autistic disorder due to a lack of 'autism-sensitive' instruments.

4.1.3 Factors for Co-morbidity

Risk factors for epilepsy in ASD have been identified as age, gender, cognitive level, type of language disorder and co-morbid medical conditions. Epilepsy is considered to be a factor for more severe presentation of ASD, however, why this relationship occurs is still not yet established (Gabis, Pomeroy, & Andriola, 2005). Steffenburg suggests learning difficulties may be a factor for the epilepsy-ASD co-morbidity (Steffenburg et al., 2003). However, this appears to be related only to childhood-onset of epilepsy (Shackleton, Kasteleijn-Nolst Trenité, de Craen, Vandenbroucke, & Westendorp, 2003). Yasuhara found a higher rate of epilepsy [43.9%] in a subgroup of those with AS from a sample of over 1,000 children and adults with ASD (Yasuhara, 2010). Inversely, the same subgroup of AS revealed a lower rate of focal epileptiform discharges compared to the extremely high rate of 85.8% of epileptiform discharges in the large sample. The extent to which these relationships can increase the understanding of the predictive value of epileptiform discharges for the co-morbidity has yet to be satisfactorily explained.

The high prevalence of intellectual disability [ID] in the autism-epilepsy comorbidity is well reported. Large scale studies have demonstrated that severe mental retardation [MR] and autism were significantly associated with onset of epilepsy in the first years of life (eg. Danielsson et al., 2009; Saemundson et al., 2007). Saemundson and colleagues (2007) reasoned that if symptomatic seizures in the first year of life are associated with MR, and MR is associated with ASD, there should be an association between symptomatic seizures in the first year of life and ASDs (Saemundson et al., 2007). They state that ASD is rarely diagnosed until after 2 years, even though seizures may already be present prior to diagnosis (ibid.). Based on evidence from multiple studies in a critical review, Spence and Schneider (2009) conclude that ID drives the association between the co-morbidity, and that ID is an independent risk factor for developing epilepsy. However, they state that while most studies report an association between ID and increased epilepsy in ASD, other studies show no significant association between epilepsy and IQ in ASD. They state that the rate of epilepsy is much higher than the general population risk even among adults with high-functioning ASD and normal IQ and therefore, while ID increases the risk of epilepsy, ASD itself is associated with a higher risk of epilepsy.

In a thorough review of children with behavioural problems, MR and epilepsy, Besag summarised that many children with epilepsy have global or specific learning difficulties, and that generally, the greater the degree of pre-existing MR, the higher the risk of developing epilepsy (Besag, 2002). Besag questions whether lower intellectual functioning in epilepsy reflects a pre-existing genetically determined deficit or a consequence of having epilepsy. Spence and Schneider (2009) highlight that the factors for an increased risk of epilepsy in ASD may not exist independently, and that an individual may have a lower IQ because of a co-morbid neurogenetic syndrome that presents with early onset epilepsy. The researchers highlight that neurogenetic disorders occur more frequently in the ASD patients with epilepsy and ID (*ibid.*).

A most interesting example which contrasts with the proposal of pre-existing neurogenetic factors for lower IQ is that of a case of MZ (monozygotic) twins with AS. Despite sharing the same DNA and environment, only the younger twin had seizures. Remarkably though, the younger twin scored higher for full-scale, verbal, and performance IQ as an adult, whereas the elder twin scored lower on all IQ measures (Ishijima & Kurita, 2007). Notably though, the younger twin was treated with AED intervention. This is important as Besag (2002) states that a learning disability [LD] must be distinguished from MR, as MR is a permanent learning disability, while a state-dependant LD is potentially reversible. Besag defines state-dependant LD as “a learning disability that is caused by factors currently affecting the individual that are potentially reversible or treatable” and severe LD with autistic symptomology can be profoundly reversed by appropriate treatment strategies such as AEDs (*ibid.*, p.110).

The presence of varying syndromes in ASD suggests a causative genetic basis. However, in high-functioning idiopathic ASD with no known genetic cause epilepsy rates are still higher than for the general population, indicating an underlying pathophysiology in ASD increasing the risk of epilepsy (Spence & Schneider, 2009). This common pathophysiological mechanism has been extended to include clinical and subclinical epilepsy and autism by some but not all researchers (Vilela, Silva, Portinha, & Correia, 2011). However what is commonly agreed is that the same brain pathology accounts for the majority of children with co-occurring ASD and epilepsy or with an epileptiform EEG (Tuchman, Cuccaro, & Alessandri, 2010). While ASD and epilepsy show phenotypic convergence in several areas, there is no single unifying phenotype, and therefore multiple biologic and genetic substrates giving rise to the phenotypes are likely. Despite the long-recognised association between both conditions, the ultimate question of causality has yet to be answered. Indeed, identifying causal mechanisms in each condition is challenging, given the high clinical and phenotypic variability. In addition, there is an on-going debate on whether the co-occurrence of one condition is

due to a secondary unrelated symptom of the neuropathological process responsible for the other condition. Several possible explanations for the co-morbidity proposed by researchers are discussed more fully in section 4.8.

4.1.4 EEG abnormalities

Early research revealed that epileptiform discharges are found in individuals with epilepsy, and are either ictal or interictal. The diagnosis of epilepsy is through the detection of interictal epileptiform discharges [IEDs], i.e. discharges between seizures, specifically because recording an epileptic seizure in clinical practice is very rare. There are four types of IEDs, defined as: Sharp Wave, Spike, Spike-and-slow-wave Complex and Multiple Spike-and-slow-wave Complexes. The controversy of IED's surrounds whether they are just very brief seizures, or fundamentally distinct from ictal discharges during an epileptic seizure. Importantly however, detection of epileptiform discharges has a very high positive predictive value for epilepsy, and IED's are fundamental for diagnosis, classification and treatment of epilepsy (Bromfield, Benbadis, Passaro, & Talavera, 2009).

It has been broadly recognised in the last decade that epileptic activity without seizures causes cognitive and behavioural impairments. The hypothesis that IEDs exert a deleterious effect on behaviour and cognition is supported by the abnormally high prevalence of IEDs in children with developmental disorders (Van Bogaert et al., 2012). Consistent with this, treating IEDs can improve behaviour (Pressler, Robinson, Wilson, & Binnie, 2005). A prevalence of IEDs ranging from 6–60.7% has been found in ASD (Chez et al., 2006). Epileptiform EEG abnormalities seem to be more common than non-epileptiform abnormalities (Spence & Schneider, 2009). More recently, higher rates have been detected possibly influenced by improved detection methods, with the highest rates found in overnight EEG recordings (ibid.). A high rate of IED's has been detected without epilepsy even in the presence of a high rate of non-epileptic seizures in children with ASD (Kim, Donnelly, Tournay, Book, and Filipek, 2006).

Muñoz-Yunta and colleagues identified epileptiform discharges in over 80% of children with ASD employing magnetoencephalogram (MEG) and importantly, were able to identify distinct differences between children with AD and AS (Muñoz-Yunta et al., 2008). Such findings were later described as surprising and challenging (Hughes, 2009). However, consistent with previous recent findings, Yasuhara and colleagues recently found a high rate of focal epileptic discharges [85.8%] in 1014 individuals with ASD (Yasuhara, 2010). The prevalence of epileptiform activity in the general paediatric population is unknown, but a recent study which set out to address this question suggests that it occurs in 1.45% of normal developing children, and that its presence may be associated with

atypical behaviour in these children (Capdevila, Dayyat, Kheirandish-Gozal, & Gozal, 2008). Clinical epileptiform discharges are common to many but not all individuals with a diagnosis of epilepsy (eg. Baise-Zung et al., 2006). For some time, IEDs have been correlated to level of cognitive functioning (Binnie & Marston, 1992). According to Muñoz-Yunta and colleagues, epileptiform discharges can be hidden and occur without any clinical seizure activity, having a profound effect on the maturing brain. Why they occur is unknown but research by Dubé and colleagues demonstrated that prolonged febrile seizures are a significant cause of IEDs in later life in animal studies (Dubé et al., 2000). Research of individuals with tuberous sclerosis complex, a condition associated with temporal lobe tubers, found that it is not the location of tubers that predicted which individuals developed ASD, but the epileptiform discharges, and early onset, persistent seizures (Bolton, Park, Higgins, Griffiths, & Pickles, 2002). Associations have been made between IEDs and severity of ASD in the studies by Yasuhara and Muñoz-Yunta and colleagues, yet the significance of this distinction remains uncertain. Fisher and Engel (2010) highlight that epileptiform EEG events during the interictal state are really fragments of seizures events and there is evidence that interictal discharges affect cognitive functioning as well as evidence of preserved behaviour during these discharges (Fisher & Engel, 2010). These IEDs are not simply benign; indeed, Fisher and Engel argue that if IEDs affect cognitive functioning, are they really “interictal”? (ibid., p.103). There is no current consensus on the presence or treatment of IEDs in ASD, and although not the focus of this research, the presence of IEDs is a remarkable feature within the co-morbidity. This research will not be employing EEG to detect spontaneous electrical activity as this will not be the focus of this research project.

4.1.5 Cumulative risk of epilepsy

Early studies revealed the cumulative risk of epilepsy and seizures in ASD, which occur regardless of epileptiform discharges (Gabis et al., 2005; Rapin, 1995). A recent study demonstrated this risk in the finding of a 24.9% prevalence of epilepsy in a sample of 345 inpatients with ASD, which increased to 58.5% in adults over 20 years of age (Parmeggiani et al., 2010). This increase contrasts with a decrease of rigid and repetitive behaviours in ASD including stereotypy, with chronological age (Esbensen et al., 2009). This reveals another inverse relationship in ASD with epilepsy which needs further investigation, as stereotypy is a characteristic of epilepsy.

4.1.6 Summary of Co-morbidity

The co-morbidity of ASD and epilepsy share a common genetic basis, common pathology, and correlate in degree of severity. However, the incidence of ASD in epilepsy is less than the incidence of epilepsy in ASD based on similar prevalence rates, raising suspicions for under-diagnosis of ASD in epilepsy. Epilepsy is not considered to be a consequence of ASD and there is a lack of epilepsy in the broader ASD phenotype. ASD is not progressive, and in fact some difficulties may resolve with

age. In contrast, a significant cumulative risk of epilepsy occurs with age, which has yet to be explained, as no evidence has been yet found for why this should occur.

According to Spence and Schneider (2009), almost nothing is known about the relationship of epilepsy to the core features of autism. Although full discussion of cognitive and behavioural deficits in the co-morbidity is not possible within this chapter, the next section will outline the co-morbidity profile in key areas. The next paragraphs will now evaluate social cognition, language and communication, and rigid and repetitive behaviours.

4.2 Social Cognition

Social cognition is defined as encompassing skills involved in the ability to recognise, understand, and appropriately respond to socially relevant information (Schacter, Holmes, & Kasteleijn-Nolst Trenite, 2008, p.181). Disruption to basic social processes is the defining feature of ASD, and social difficulties are profound, appearing in early infancy (Volkmar, 2011). Lorna Wing (1981) suggests that those with ASD lack the ability to understand the rules of social behaviour. Research investigating stress in children with and without ASD during an ecologically valid benign social interaction found that those with ASD had significantly higher cortisol levels, reflecting enhanced arousal from social engagement (Corbett, Schupp, Simon, Ryan, & Mendoza, 2010). Structural abnormalities found in the autistic amygdalae have been identified, which is significant as the amygdalae play an important role in social and emotional engagement (Toal et al., 2010). In epilepsy, social cognitive functioning may be influenced by neurobiological, psychosocial, and psychologic factors (Schachter et al., 2008). According to García-Peñas (2009) there is a disproportionate presence of ASD in TLE, possibly due to damage to the amygdala and related temporal lobe structures responsible for social brain functioning, mainly amygdala, hippocampus and superior temporal sulcus. The researchers state that TLE perturbs the development of brain systems that underpin social intelligence during a critical early stage of brain maturation, thereby inducing ASD. Specifically, people with epilepsy have difficulties with interpersonal relationships, and specific areas of dissatisfaction are social isolation, forming friendships, and participating in social activities (McCagh et al., 2009). Children with epilepsy tend to be withdrawn, socially isolated and hyperactive, and this is significantly related to epilepsy type and frequency. Poorer psychosocial well-being has also been related to escape-avoidant coping styles in adults with epilepsy (Goldstein, Holland, Soteriou, & Mellers, 2005). Consistent with these studies, successful surgery for epilepsy significantly improves social functioning (Lach et al., 2010). Other researchers highlight psychosocial factors as a strong factor for social difficulties in epilepsy (Smith et al., 2009; McLaughlin, Pachana, & McFarland, 2008). McLaughlin and colleagues point out that although more than two thirds of their sample have

less than one seizure a year, frequent seizures and increased perception of stigma that is associated with epilepsy have been negatively correlated with QOL and reduced psychosocial functioning (ibid.). The researchers state that it may be the apprehension induced by the possibility of a seizure that reduces health-related QOL. The stigma scale in their research asks adults with epilepsy to state whether they felt that other people were uncomfortable with them, treated them as inferior and preferred to avoid them. However, the researchers did not account for the individuals with mTLE, a common epilepsy type, who are impaired on advanced social cognition and tasks of ToM, and who are unlikely to be able to accurately read emotional and social cues to gauge whether other people are uncomfortable with them. Even so, the extent to which improved social outcomes in epilepsy can be attributed to cognitive factors rather than psychosocial factors is still unknown.

Face processing and recognition are a major component of social interaction. Impairment of eye gaze expression, face and facial emotion recognition, and processing of inverted faces is well reported in both disorders (Schacter et al., 2008; Volkmar, 2011). While impaired face emotion recognition is commonly found in TLE, it has further been related to ToM deficits for childhood-onset (Meletti et al., 2003). However, research of social cognition has been criticised for lack of ecological validity. Of note, where impaired eye-gaze in a newborn infant with ASD is unexplainable by a delayed ToM, abnormal eye gaze occurs at onset of neonatal seizures in epilepsy (Panayiotopoulos, 2005). Further, gaze deviation can occur with focal temporo-parieto-occipital or hemispheric seizures in epilepsy which may be related to epileptiform discharges without seizures (Kaplan, 2005, p.977). This kind of evidence suggests that different explanations are needed for abnormal eye gaze in those with ASD who have epilepsy, compared to those who do not. Research into social interactive behaviour of autism has primarily focused on eye contact and gaze aversion. On the one hand, it has been found that those with ASD focus on the mouth rather than the eyes of a speaker, which may suggest that they are motivated to participate to retain social interaction. On the other hand, the over attention to an inanimate environment that has been documented and discussed by Volkmar implies lack of social responsivity or motivation, and should be a serious concern (Volkmar, 2011).

Wolf and colleagues (2010) highlighted 3 independent components for understanding dynamic socio-emotional information in a naturalistic, non-laboratory setting: self-referential mental activity, face processing and recognition, and language comprehension. Self-referential mental activity involves self-reflection for attributing mental states to others. The ventromedial prefrontal cortex [vmPFC] is implicated in self-referential processing related to judgements and inferences about the self and others. In ASD, fMRI has helped identify atypical neural self-representation, evident through reduced functional connectivity between the vmPFC and associated areas (Chakrabarti et al., 2009). Further, the degree of this difference, when compared to a control group, strongly related to the degree of

social impairment in early childhood in ASD. A recent fMRI study by Wang and colleagues (2011) examined functional connectivity differences in patients with generalised tonic-clonic seizures. The researchers found both increased and decreased functional connectivity between seizures in the resting state networks. Functional connectivity in the right medial prefrontal cortex was found to correlate with epilepsy duration. The researchers suggest that decreased functional connectivity in the medial prefrontal cortex indicate that seizures may reorganise the basic networks which are of central importance for understanding the social world, with severe negative consequences. The medial prefrontal cortex is a crucial component of the neural systems mediating social knowledge which contributes to constructing an understanding of the social world (Krueger, Barbey, and Grafman, 2009). Taken together, the evidence above illustrates that individuals with epilepsy even from early infancy have a range of social difficulties relative to epilepsy type and duration, which may be underpinned by brain structural changes and functional differences. Further, epilepsy duration may impact upon the neural systems crucial to social and emotional processing.

4.3 Language and Communication

Communication is the exchange of ideas and feelings between people, generally through speech or writing. A defining characteristic of ASD are speech and language difficulties. A number of studies have shown that epilepsy and seizures are associated with speech arrest or mutism, dysarthria, impaired articulation of speech, echolalia or repetitive speech, and abnormal verbalization. Sub clinical epilepsy effects language, severe language regression is a feature of acquired epileptic aphasia (Tuchman & Rapin, 1997). This suggests that co-morbidity may account for language aphasia in AR, In contrast, left-hemisphere dominated language abilities implies intact language function in right-hemisphere epilepsy. In fact this is not the case, as contralateral deficits are found in all chronic unilateral TLE (Seidenberg et al., 2005). Idiopathic language deterioration can occur in association with seizures, EEG epileptiform activity, and sub-clinical epilepsy; importantly though, anti-epileptic drugs can be helpful for improving language functioning (Holmes & Riviello, 2001; Tuchman & Rapin, 2002). Epileptic activity in the brain can affect language development in children. Even when children with epilepsy have a good understanding of language, they find it difficult to express themselves (Svoboda, 2004). According to Overvliet and colleagues, nocturnal epileptiform EEG discharges and nocturnal epileptic seizures in children with epilepsy will cause or contribute to diseased neuronal networks involving language which are less efficient compared with typical neuronal networks (Overvliet et al., 2010). Generally though, the incidence of speech and language problems in epilepsy is not known and more common than is generally suspected, and therefore overlooked (Svoboda, 2004, p.11, p.13). Such evidence suggests that communication, especially language, is impaired in epilepsy. This may be due to impaired neuronal networks involving language,

affected by epileptiform discharges and epileptic activity. The extent to which this impairment is common to all individuals with epilepsy has yet to be established.

4.4 Rigid and Repetitive Behaviours

Repetitive behaviours are a core characteristic of ASD, and restricted, repetitive and stereotyped patterns of behaviour are part of the diagnostic criteria for autism. According to Bodfish and colleagues, repetitive behaviours in autism are a pervasive feature, and the severity of repetitive behaviours and of motor dysfunction predicts severity of autism (Bodfish, Symons, Parker, & Lewis, 2000). Consideration needs to be given to the fact that epileptic seizures are ‘stereotypic’ events (Schacter et al., 2008, p.139). Repetitive motor actions are a feature of focal seizures of medial temporal lobe origin (Duncan, 2005). According to Tononi & Koch (2008) repetitive behaviours such as tapping or counting can continue during seizure activity, and remain unhindered. Unsurprisingly, Tuchman & Rapin (2002) highlight how unusual repetitive behaviours, common in children with ASD, can be difficult to distinguish clinically from seizures. However, recent evidence in animals by Kleen and colleagues has indicated a strong relationship between seizures and some RRBs, as it was demonstrated that those with early-life seizures show impaired behavioural flexibility in later adulthood (Kleen et al., 2011). Taken together, this evidence suggests that some components of RRBs may indicate either the presence of active epilepsy, or that early-life seizures have occurred in an individual. Conversely, a lack of stereotypic RRB’s in an epilepsy population may indicate that early-life seizures have not occurred or they may indicate some level of recovery from epilepsy. However, such recovery doesn’t rule out the re-emergence of epilepsy in later life. Indeed, several studies have found a significant relationship between early-life seizures and a greater risk of epilepsy in later life (Cendes & Andermann, 2002; Dubé, Brewster, Richichi, Zha, & Baram, 2007).

Unity of Core Components

Happé and colleagues point out that the 3 core characteristics evaluated above are relatively independent of each other (Happé et al., 2006). They argue that RRBs are not good markers of autism in infancy and they emerge later than social and communication difficulties, and are not good predictors for measures of imitation or language (ibid.). However, as the presence of RRB’s is necessary for a diagnosis of ASD, this argument suggests that all 3 core characteristics are crucial for the ASD diagnosis, but that RRBs are different from social and communication difficulties as they emerge later. There are difficulties with exploring this argument in adults with epilepsy, primarily as RRBs are not well-researched, and the literature review did not reveal a single study exploring RRBs in an epilepsy sample, therefore the presence of RRBs have yet to be established.

Social difficulties in epilepsy are not well-researched, and it is unknown whether onset of social difficulties correlates with onset of epilepsy. However, onset of speech and language difficulties can precede the onset of seizures in childhood epilepsy (Svoboda, 2004, p.15). Alternatively, they may develop at the same time or following seizure onset, and they are most apparent during stress.

The evidence in sections 4.2 to 4.4 suggests that the core characteristics of ASD are commonly detected in individuals with epilepsy. However, what is not known is whether all individuals with epilepsy are deficit in the triad of core components and therefore the triad of impairments are common to all individuals with epilepsy, or whether some core characteristics are found only in specific epilepsy types. Overall, until the extent of autistic traits and characteristics has been established in epilepsy, the relationship of the core ASD characteristics to each other and to the onset of epilepsy has yet to be identified. Clearly, further research of ASD in children with epilepsy and children who are recovering from epilepsy would be extremely valuable. A report recently submitted to the American Psychology Association by Dezort and Fisher (yet to be published), found that 77% of children with epilepsy presented with a developmental delay, and 36% presented an identifiable ASD. This prompted and Berg and colleagues have recently called for ASD screening *in all children with epilepsy*, which could provide more definitive evidence for the co-morbidity in the future (Berg et al., 2011).

4.5 Other Cognitive and Behavioural Similarities

Research of behavioural characteristics of adulthood-onset epilepsy is lacking, and there is a remarkable lack of systematic studies on the behavioural characteristics of childhood epilepsy (Besag et al., 2008). Even so, in addition to the core behaviours evaluated in this chapter, consistent evidence demonstrates that other characteristics that are associated with the co-morbidity include memory, motion perception, recognition and familiarity, motor function, executive functioning, and attention, which occur to varying levels of severity. For example, impairment of movement performance and atypical sensory integration has been found in ASD and TLE (Siaperas et al., 2011; Grant, 2005). Impaired attention is a frequent complaint in epilepsy. For example, adults with FLE and TLE have impaired performance for tasks of sustained attention and divided attention (Schacter et al., 2008, p.157). Studies of patterns of behavioural characteristics of adults with epilepsy remain controversial. Devinsky and Najjar (1999) argue against a personality disorder in temporal lobe epilepsy, the most commonly diagnosed epilepsy type. They point out that the existence and specificity of behavioural characteristics are incongruous, as there are too many factors which interact, and that behaviours are poorly defined. Swinkels, Kuyk, van Dyck and Spinhoven (2005) state that while many epilepsy patients do not meet criteria for a specific personality disorder, they

show some typical personality oddities that are not necessarily maladaptive. An earlier study by Bear and Fedio (1977) aimed to develop a personality trait inventory consisting of 18 traits for TLE: the Bear-Fedio Inventory (BFI). All 18 traits were increased in patients with TLE compared to healthy or neurological controls. Unfortunately, although the concept of TLE traits would be useful, the study has been criticised for the limited sample size and lack of control for AEDs or other co-morbid disorders.

However, the following extract of 5 of 18 interictal personality traits of TLE is of interest to the co-morbidity of epilepsy and ASD:

Trait	Clinical observation (TLE), <i>without seizure activity</i>
Viscosity	Stickiness, tendency to repetition
Circumstantiality	Loquacious, pedantic, overly-detailed
Hypergraphia	Keeping extensive diaries, detailed notes
Obsessiveness	Ritualism, orderliness, compulsive attention-to-detail
Hypermoralism	Attention to rules with inability to distinguish significant from minor infraction

From Swinkels et al., (2005, p.46)

One consideration of this study is that the remainder of the BFI traits may not be strongly related to ASDs, and further research is needed to establish the extent of the remaining traits in both epilepsy and ASD. However, individuals with epilepsy were not found to spontaneously offer descriptions of these traits. This may be a result of verbal expressive deficits and difficulties communicating meaning through language (Svoboda, 2004, p.144). As such, caution must be used by researchers when interpreting ‘meaning’ from language used by individuals with epilepsy to avoid errors inferred by the researcher. Generally, the aim of this research is to identify ASD characteristics and traits in adults with epilepsy, and not to show that each condition is identical. After these traits have been identified, it would be pertinent to examine the extent of other reported BFI traits in each condition. In addition, the BFI has yielded mixed results so it can only be concluded that some traits are found more in people with epilepsy than in the general population (Swinkels et al., 2005). However, the researchers highlight the overlap with obsessive-compulsive disorder which appears to be consistent with previous studies, and state that well-controlled studies with valid and standardised diagnostic instruments are needed (ibid.). A heightened attention-to-detail, a feature of ASD, has been noted in individuals with TLE, although research on what underlies this has been lacking (Herzog, 1999, p.114). A more recent study by Harden and colleagues (Harden et al., 2009) compared personality

type in adults with epilepsy or with non-epileptic psychogenic seizures. An unexpected surprising finding was a high rate (44%) of avoidant, dependent, and obsessive-compulsive personalities in epilepsy patients. The researchers question whether this personality style is related to the genesis of epilepsy itself or a reaction to living with the condition.

The evidence outlined above suggests that specific behaviours may be related to specific types of epilepsy, such as TLE. In the face of such evidence of a TLE personality, it needs to be remembered that TLE is often refractory. This could implicate AEDs in the masking of socio-emotional difficulties in the non-TLE patients. Such evidence makes the investigation of social cognition imperative, as it suggests that if AEDs mask social cognitive differences, impaired social cognition may be universal to all epilepsies.

ASD is characterised by hypersensory symptoms which are considered to be a common feature of the disorder (Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009). Some researchers have even proposed that such hypersensitivity underlies the cognitive differences of ASD. Baron-Cohen and colleagues argue that sensory hypersensitivity is the origin of attention-to-detail in ASD, which ultimately underpins hyper-systemizing abilities (Baron-Cohen et al., 2009). The researchers hypothesise an enhanced perceptual functioning model of ASD characterised by superior low-level perceptual processing. While evidence suggests that hypersensory symptoms are frequently found in ASD, they cannot specifically differentiate ASD from other developmental disorders (Rogers & Ozonoff, 2005). Even so, such evidence appears to be consistent with sensory differences in individuals with epilepsy. A review of perception in epilepsy has led Schacter and colleagues to speculate whether interictal epileptiform discharges also play a causative role in disturbances of somatosensory, auditory, visual perception, and hypersensitivity to visual perception, which are well-documented (Schacter et al., 2008, p.126, p.173). Certainly, tactile differences indicating severely impaired somatosensory processing led Grant and colleagues to conclude that individuals with epilepsy may have supranormal sensory thresholds, which may be specific to TLE (Grant, Henry, Fernandez, Hill, & Sathian, 2005). Such evidence is consistent with findings of a suprathreshold for vibrotactile stimulation in ASD reviewed by Baron-Cohen and colleagues (2009). Early research by Bear (1979) proposed that hyperosmia, an intensification of smell which can be a characteristic of TLE, may be indicative that TLE is a syndrome of sensory-limbic hyperconnection. Supporting evidence for this is provided by Hermann and Chhabria which hints at this hyperconnection being related to the ictal stage of epilepsy (Hermann & Chhabria, 1980). Additionally, findings of both increased and decreased functional connectivity in the primary visual cortex have led researchers to conclude that specific perceptual functions are impaired in TLE even when there is no seizure activity

(Zhang et al., 2009). Importantly though, evidence of hyper-responses to somatosensory evoked potentials found in those with JME and progressive myoclonic epilepsy suggests that epilepsy rather than TLE may be related to hypersensory functional connectivity (Kochen, 1993). Baron-Cohen and colleagues propose that hypersensitivity in ASD could arise from differences of sensory processing at several levels (Baron-Cohen et al., 2009). However, perhaps an overlap of hypersensory processing in the co-morbidity is unsurprising, given the functional connectivity similarities in the co-morbidity (see 3.10), and given that brain structural similarities are found in those with ASD that are similar to adults with MTLE (see 3.5).

Generally, the evidence reviewed in section 4.5 above suggests an overlap of cognitive and behavioural symptoms in the co-morbidity; however these symptoms are not considered necessary or sufficient for a diagnosis of ASD.

4.6 Treatment

Given the common pathology between the co-morbidity, it is no surprise that treatments for epilepsy reveal significant improvements in those with ASD. There have been several studies of AED use in children with ASD without epilepsy that have shown improvements in core symptoms of ASD (Di Martino & Tuchman, 2001; Muñoz-Yunta et al., 2008). Continual improvements have been also found in children with autism without epilepsy even after the AEDs were discontinued (Baird, Robinson, Boyd, & Charman, 2006). A randomised, double-blind, placebo-controlled trial found that the AED ‘Valproate’ may be effective in the treatment of mood changes in children and adolescents with ASD (Hollander et al., 2010). The researchers suggest that improved behavioural response may be due to the treatment of underlying epileptiform abnormalities.

In their literature review of AED use in ASD, Di Martino & Tuchman (2001) found evidence of improvement in two of the core features of autism, communication and socialisation which occurred regardless of seizure control. Improvements in behaviour and communication were also found to correlate to epileptic discharges or epilepsy in ASD. Importantly, the researchers propose that this suggests common neuroanatomic and neurochemical neural circuits within epilepsy, language and behaviour. This suggests a common relationship in which epilepsy is related to language and behaviour rather than RRBs. Further, ASD, epilepsy and affective disorder may share a common neurochemical substrate which leads to improvements after AED intervention in those with ASD. These findings can be compared to research by Happé and colleagues (Happé et al., 2006). Happé and colleagues found that while the 3 core features of ASD may be independent, RRBs are different from social and communication difficulties as they emerge later and are not good predictors of other

autistic characteristics. Taken together, such evidence suggests a relationship between affective behaviour and communication to ASD and the presence of epilepsy, which may be distinct to that of RRBs. This may implicate neuronal connectivity with some but not all autistic characteristics in epilepsy and ASD as dependent on the brain maturation process. However, the influence of epilepsy and epileptic discharges during the maturation process of the brain across the lifespan has not yet been determined. As the relationship of AEDs to ASD is not clear, the widespread use of AEDs in children with ASD but without seizures is not recommended until further research supports their usage. Specifically, Yasuhara presents the case for the requirement of a double-blinded study providing evidence for quantitative improvement of autistic characteristics through AED intervention (Yasuhara, 2010). It should be added that satisfactory explanations for why autistic children without seizures are being successfully treated with anti-epileptic drugs are lacking. Other treatments for epilepsy such as surgery, VNS and the ketogenic diet demonstrate some additional successful outcomes, but studies are limited.

4.7 Challenges

ASD and epilepsy are different conditions that appear to share a common pathology. Within the co-morbidity, it is hard to reconcile obvious differences such as the M:F ratio, developmental or acquired features of epilepsy, life-long or recoverable features of epilepsy, and the debate surrounding whether resolution of epilepsy implies improvements of autistic characteristics in ASD. The M:F ratio differences are particularly puzzling. However, it is commonly known that males have a highly vulnerable epileptic brain. In 2000, Briellmann and colleagues explored this association employing MRI in males and females with TLE (Briellmann, Berkovic, & Jackson, 2000). Their research indicated that males are more prone to severe brain abnormalities from seizure activity in which seizure frequency is a factor, resulting in more brain damage in males. Research from animal studies have revealed that the developmental profile of the seizure threshold is under the control of early postnatal testosterone surge in male but not females rats, which suggests biological factors for increasing the likelihood of seizures (Velisek, Veliskova, Giorgi, & Moshe, 2006). However, such findings are not evidence for biological origins of psychological traits of adults with epilepsy and importantly, these psychological traits are not yet fully identified or well-defined. Although this does not provide an explanation for the M:F ratio differences, it poses a poignant question on whether males and females might recover differently from febrile seizures regarding cognition and behaviour. While the concept of ASD as a developmental life-long condition has recently been challenged again by a large-scale study, such findings are incompatible with the theoretical and diagnostic view of autism as a developmental disorder (Zappella, 2010). Further, the lack of heritability of epilepsy does suggest different causes for a common aetiology. Finally, if they share a common aetiology, why is epilepsy cumulative in ASD?

4.8 Explanations for co-morbidity

While it has been suggested that subclinical epilepsy may cause AR or that there may be a causal relationship between benign focal epilepsies and AR, researchers agree that this relationship remains unclear (Tuchman & Rapin, 2002; Baird et al., 2006). It has also been suggested that children with frequent epileptiform discharges in their early years are liable to have permanent ASD (Tuchman et al., 2010). The explanation of a relationship of ASD to the medial temporal lobe does not explain why epilepsy may be cumulative in ASD. On the one hand, there may be an under-diagnosis of epilepsy due to inability of autistic children to co-operate with clinical investigations such as EEG; however on the other hand, clinicians are finding an under-diagnosis of ASD in epilepsy. Further, it is not known how recovery from undetected epilepsy presents across a life-time in terms of autistic characteristics. Although there is some suggestion of permanent ASD in children with epilepsy, there has been no systematic follow-through on recovery from childhood epilepsy employing psychological assessment tools. Overall, this suggests that this is not a clearly defined co-morbidity, and the behavioural relationship between the two is ill-defined. One reason may be that epilepsy is poorly defined in terms of behavioural differences compared with a matched control group, both in childhood and adulthood, and psychological research between those with and without epilepsy is lacking. An explanation for this may be that research is neurologically, physiologically or pharmaceutically biased, or that researchers themselves may be wary of studying individuals with epilepsy.

In 2006, Deonna and Roulet-Perez outlined possible explanations for the co-morbidity:

Both conditions are totally independent

The same brain pathology is at the origin of an autistic phenotype and epilepsy

An epileptic process occurring in early development interferes with the developing function of specific brain networks involved in communication and social behaviour

A focal (multifocal) brain pathology (i.e., tuberous sclerosis) that affects frontal or mesiotemporal structures (limbic system) can be at the origin of an autistic phenotype as well as the trigger of an epilepsy that aggravates the autistic symptoms

An epileptic process causes a specific sensory or cognitive dysfunction with autistic withdrawal in a vulnerable child

(Deonna & Roulet-Perez, 2006)

It is clear that interictal epileptiform discharges without epilepsy are strongly correlated to the presence and severity of ASD in those with only ASD (Yasuhara, 2010). It is also clear that epileptic activity is strongly correlated to the presence and severity of ASD in those with ASD and epilepsy (Gabis et al., 2005; Tuchman, 2006). However it is not clear whether epileptic activity is strongly

correlated to the presence and severity of ASD in those with only epilepsy. So far this relationship is unclear, and one explanation may be that epilepsy is poorly understood and there is a remarkable lack of well-validated studies of behaviour in epilepsy. Despite an extensive body of research examining cognition and behaviour in both autism and epilepsy, the findings in epilepsy have not been consistent, mostly likely because epilepsy is comprised of a heterogeneous spectrum of symptoms, and cognition and behaviour is best explained by functional network differences. Even so, the review in this chapter reveals autistic-like characteristics in those with epilepsy which is consistent with previous reports that cognition and behaviour is difficult to distinguish between the two conditions. Essentially, the argument for identifying autistic characteristics in both TLE and most childhood-onset epilepsies is strong. But more to the point, researchers argue that behavioural changes can occur in patients with other epilepsies such as JME, absence epilepsy, FLE, insular cortex epilepsy and tonic-clonic seizures, which overlap with features of TLE making the investigation of autistic characteristics in epilepsy even more compelling (Devinsky & Najjar, 1999; Nguyen et al., 2009). This is consistent with existing arguments that ASD may be under recognised in epilepsy. However, whether the epileptic seizures may intrinsically have a role in the manifestation of autistic characteristics remains unknown.

4.9 Assessment method

The review suggests that even though there are unexplainable differences in the co-morbidity, a high presence of similarities have been identified; lending weight to the proposition that ASD may be under recognised in epilepsy. In order to consider why this might occur, an inspection of the way in which ASD is identified in epilepsy is required. A good assessment must have three qualities: validity, discrimination and reliability. Validation is the process of establishing the degree of accuracy and precision of an instrument to recognise observations that apply to real situations. However, there are several reasons to suspect that current psychological assessment methods fail to detect autistic characteristics in epilepsy in a valid manner. Differences of ictal, interictal and subclinical behaviours present difficulties for assessment. From the early days of behaviour and personality assessment, it was suggested that several epilepsy types were not uniformly benign conditions. Aicardi provides an example of how current methods fail to detect IQ problems in epilepsy which can often be nearly normal without epilepsy, but severely impaired during epilepsy (Aicardi, 1999). Validation of assessment has been highlighted in a discussion between Janz and Besag, who emphasise the importance of the timing of assessments in epilepsy (Besag, 2004). Krishnamoorthy highlights specific methodological problems when evaluating psychiatric co-morbidity in epilepsy (Krishnamoorthy, 2006). He states that most instruments are not developed for the specific psychopathology in epilepsy, but have cut-off scores that may not be valid for the epilepsy population; there are no valid epilepsy-specific measures of behaviour; and that interview based measures may be

inaccurate. Steffenberg additionally highlights concerns, proposing that ASD may be overlooked due to lack of sensitive instruments to assess ASD in epilepsy (Steffenberg et al., 2003). There is a need to firmly establish a more valid and accurate research method of assessment which is epilepsy-specific for individuals with epilepsy.

4.10 Development of a new method of assessment

It needs to be acknowledged that individuals with epilepsy need special consideration when administering standard psychological tests. The method employed for current assessments suggest that individuals may be reporting on abilities either during epileptic activity or interictally. Epileptic activity significantly impacts on cognition and behaviour, however without discrimination of epileptic stages, any measurement cannot be scientifically valid. Further, according to Krishnamoorthy, the extent of difficulties may be under-reported as clinical indications suggest that even cognitively unimpaired individuals with epilepsy under-report their psycho-pathology, particularly during a seizure aura (Krishnamoorthy, 2006). This may be due to the complexities of evaluating behavioural difficulties in individuals with epilepsy, possibly worsened with the presence of language comprehension and expression difficulties. By discriminating between ictal and interictal stages, the genuine psychological effects of epileptic activity may be revealed, therefore increasing validity. But to what extent is this possible?

Structured questionnaires with rating scales can be valuable for identifying behaviours during seizure activity by addressing the patients difficulty in describing and recollecting symptoms, reflecting on behaviours and subjective symptoms of an aura that might be forgotten, and to describe symptoms that might otherwise be too normal or too unusual to be reported (Nakken et al., 2009). Studies of behaviour for interictal periods and seizure auras have previously been vulnerable to methodological problems. Mungas and colleagues investigated the reliability and validity of rating scales for assessing behaviour change in epilepsy by comparing two questionnaires, the BFI (see section 4.5) and the BRSE 'Behavior Rating Scales for Epilepsy' (Mungas, Blunden, Bennington, Stone, & Palma, 1990). The BFI was one of the first attempts to analyse behaviour in TLE employing a self-rating inventory for assessing the interictal period. The following paragraph reports concerns regarding the reliability and validity that were raised in their investigation which could also be concerns for the seizure aura stage.

Mungas and colleagues highlighted concerns that replication of the BFI produced mixed results, however by comparison, good interrater reliability, clear convergent validity, and favourable evidence of discriminant validity was shown by the BRSE (Mungas et al., 1990). Therefore the criticism of

reliability is not a concern for all self-rating assessments in epilepsy. Concerns regarding whether a prodrome or an aura was being reported were also highlighted. However as noted earlier, prodromi are not a consideration of this research project, and according to Fisher and Engel (2010), individuals usually retain the ability to identify the start and end of the sensation phenomenon that mark their seizures. Diagnosis or classification of TLE was a concern for the researchers, and this should relate to all investigations where epilepsy type is investigated. However recent improvements have been demonstrated through employment of neuroimaging and V-EEG to facilitate the identification and diagnostic accuracy of epileptic seizures. Mungas and colleagues demonstrated that a large percentage of variance in the BFI traits can be accounted for by the presence or absence of other co-morbid disorders rather than indicating the presence of a specific behavioural syndrome in TLE. However, until the extent of other co-morbid disorders have been fully identified, it could also be argued that it is possible that some characteristics are being missed in the epilepsy condition. Importantly though, when identifying a specific epilepsy type, the consideration of a secondary identified or unidentified seizure type should be a consideration. Additionally, the lack of construct validity as a measure of behaviour specifically associated with TLE may now be partly explained by recent evidence which suggests that TLE is a network disorder which has symptoms that overlap other epilepsy types. Differing degrees of brain damage and the site and location of any brain lesions have been highlighted by many researchers as methodological difficulties that may be impossible to overcome. However, while degrees of brain damage may be overcome by sample exclusion, more recently epilepsy has been considered a network disease reflecting abnormal functional networks rather than origin of onset. A behavioural assessment during the seizure aura stage would provide a measure of the effect of seizure activity on these networks. The range of the behavioural spectrum would be consistent with the proposal by some researchers that epilepsy is a spectrum disorder, and it might be argued that its defining characteristics are still under investigation. Mungas and colleagues state that despite the previous theoretical difficulties highlighted with behavioural assessment, the development of behaviour rating scales to assess epilepsy will be important. They state that the BRSE scales provide a relatively quick and effective method for researching behavioural aspects of epilepsy, although difficulties may occur where there is conceptual complexity requiring difficult judgments to be made. It remains a consideration that reliability of behavioural measures may be hindered over time, as enduring deficits attributed to localised brain structural damage can resolve over months or years (Fisher & Engel, 2010).

Much empirical evidence has shown that, where possible, individuals with epilepsy can reliably report what happens during a seizure aura (Jan & Girvin, 2008). Fogarasi and colleagues (Fogarasi et al., 2007) found that seizure aura activity is independent of the brain maturation processes. Therefore, the new method will specifically discriminate between scores for two epileptic stages, the seizure aura

stage (ictal), and without seizure aura stage (interictal) (see 2.7.1 for definition). The difference in these two scores will reflect the impact of a single mild epileptic seizure, and indicate any specific area for loss of ability. This method may prove useful for investigating whether behaviour is related to the genesis of epilepsy, or from living with the condition, especially where analysis of factors such as seizure frequency or age at onset are conducted for each stage. One limitation of employing this method is the assumption that behaviour in epilepsy is not congruent with a continuum of fluctuating levels of epileptic activity, but is a dichotomy. Further, up to 26% of seizure auras can go unreported in adults (Hoppe et al., 2007). However, this assessment method does not invalidate the concept of a continuum of ability, but offers the next best method based on current evidence until there is further consensus for interictal behaviours, for example, behaviours directly attributed specifically to IEDs.

As seizure auras and the epileptogenic zone are so closely related, seizure auras can be clinically classified according to their localizing and lateralizing value by employing international guidelines for the classification of epileptic seizures (CCTILAE, 1981). However, while this classification is useful, many researchers find a very high rate of non-specified auras which do not fit into neat descriptions (eg. Nakken et al., 2009). Therefore, this research project will not attempt to classify participants' seizure auras or discriminate between isolated and non-isolated seizure auras. The research will not review medical records, or review clinical interviews for confirmation or characteristics of seizure auras due to difficulties with information elicited from interviews. This method will be highly appropriate for psychological assessment during research into epilepsy and may ultimately be a useful tool for the administration of assessments. It aims to provide a better understanding of the impact of seizure activity as an epileptic stage on cognition and behaviour. This supports the notion that investigations of seizure auras could yield important and reliable information about epileptic activity.

Chapter 5

Autistic Traits in Epilepsy

5.1 **Experiment 1: Autism Spectrum Quotient [AQ]**

5.1.1 Background

The literature review in Chapter 4 presented evidence which suggests that there is some reason to suspect autistic-like characteristics in adults with epilepsy, especially TLE, where there is no diagnosis of any ASD. Despite the theoretical rationale, the relationship of epileptic activity and these characteristics have not been well investigated. The first aim of this research is to establish the extent to which these characteristics are genuinely associated with epilepsy, and Chapters 5 and 6 will undertake a series of initial experiments to establish this relationship. Anecdotal and empirical evidence suggests that cognition and behaviour in epilepsy is consistent with some patterns found in those with ASD. The question as to whether this is due to the condition of having epilepsy, or the effect of epileptic activity upon the brain is unknown. Experiment 1 will assess adults with epilepsy for autistic traits, as very little is known about the relationship of epilepsy to the core features of autism, or about the prevalence of ASD in adulthood-onset epilepsy.

Importantly, the relationship of seizure aura activity to the presence and severity of autistic characteristics has not yet been fully investigated in individuals who do not have a diagnosis of ASD. Where autistic characteristics have been identified in individuals with epilepsy, it is presently unknown whether these autistic traits occur as a result of having epilepsy, or specifically as a result of epileptic activity. For example, there is some evidence that epileptiform discharges may impact upon language (Tuchman & Rapin, 1997). However, seizure aura characteristics can be associated with a variety of clinical manifestations, and specific behavioural outcomes of seizure auras are still under debate. If autistic characteristics are due to the condition of having epilepsy, this implies that individuals with adulthood-onset can acquire these characteristics, which contrasts with the concept of ASD as a developmental disorder. This would reveal a clear distinction between ASD and epilepsy. If these characteristics are related to epileptic activity, it implies that autistic characteristics are dynamic, which contrasts with the concept of autistic characteristics as a stable, life-long condition. In contrast to the broader phenotype of autistic traits, epilepsy is a network disease which can occur at

any age, and is largely non-idiopathic without any identifiable cause. However, recent evidence suggests that the subtle cortical structure changes in TLE may indicate the existence of a common neuro-developmental phenotype (Voets et al., 2011). This suggests that for TLE alone, any significant findings may contribute to disentangle the neuro-developmental basis for ASD and epilepsy. The new method will be useful for addressing the extent to which known seizure activity affects autistic characteristics. Research has previously identified factors influencing cognition and behaviour in individuals with epilepsy as seizure frequency, severity and type, and childhood-onset of epilepsy (Aicardi, 1999; Meletti et al 2009). Childhood-onset epilepsy has previously been defined as onset under 18 years of age (eg. Shahar & Genizi, 2008). These factors will therefore be explored further.

One well-recognised measure of autistic characteristics is the Autism Spectrum Quotient (AQ), a questionnaire designed to quantify the extent of autistic traits in the general population by assessing 5 subscales: social skills, attention switching, imagination, attention-to-detail, and communication. The AQ was developed to measure the degree to which an adult with normal intelligence has autistic traits. Despite strong evidence that males often demonstrate higher autistic traits than females in the general population and also among those with ASD, no significant difference in autistic traits were found between gender in the original study among the AS/HFA group (Baron-Cohen et al., 2001, p.5).

ASD and epilepsy share a common genetic basis, thereby common traits already exist. The AQ will be employed to investigate social and non-social autistic characteristics in adults with epilepsy measured as traits in the ‘without aura’ condition. Evidence suggests that epileptic activity during seizures may ‘induce’ rather than merely ‘stimulate’ some autistic characteristics in epilepsy (Bonora et al., 2011; Gabis et al., 2005; Tuchman, 2006). However, while this relationship implicates seizure activity, it has not been directly investigated. Any relationship of autistic traits to seizure auras does not necessarily indicate that auras cause autistic traits during seizure auras, nor does it imply that seizure aura characteristics are permanent. The measurement of changes to traits during the seizure aura stage appears contradictory, as autism is a genetic developmental disorder. However, its relationship will be demonstrated by the influence of seizure auras to pre-existing traits in the ‘with aura’ condition. Notably, this research does not seek to diagnose individuals suspected of having ASD, and therefore other diagnostic assessments will be discounted.

AQ Subscales

The literature review has not revealed any research for imaginative abilities in individuals with epilepsy. This is surprising given that individuals with impaired memory typically display poor imagination, and that the medial temporal lobe is typically engaged during imagination, which may have implications for those with MTLE. Attention-switching, which is a measure of cognitive flexibility, is a component of executive functioning. Decreased executive functioning abilities have been found in children with epilepsy and across nearly all epilepsy syndrome groups (Høie, Mykletun, Waaler, Skeidsvoll, & Sommerfelt, 2006). Attention deficits are commonly reported in epilepsy (Svoboda, 2004, p.270). Only one study has demonstrated lower scores on tasks involving attention control processes such as cognitive flexibility and inhibitory processes in children with epilepsy (Deltour, Quaglini, Barathon, De Broca, & Berquin, 2007). At present there is little evidence to demonstrate that imagination or attention-switching is impaired in epilepsy. However, there is evidence for poor social functioning and psychosocial adjustment in epilepsy (Gois et al., 2011; Marin et al., 2008; McCagh et al., 2009). Some researchers have suggested that functional connectivity differences in individuals with epilepsy indicate that seizures may reorganise the networks important for understanding the social world with severe negative consequences (Wang et al., 2011). Changes in ‘functional connectivity’ during a seizure aura may provide an alternative theoretical possibility for any relationship between the autistic traits measures and seizure activity. In 2008, researchers found that for individuals without TLE, personality traits and psychiatric symptoms associated with the interictal TLE personality could be found among non-clinical individuals, possibly as the result of hyperconnectivity (Aycicegi-Dinn, et al., 2008). This suggestion is consistent with previous suggestions that sensory-limbic hyperconnections generate the behavioural profile of TLE and possibly some other epilepsy types (Persinger, 1987; Bear, 1979; Kochen, 1993). Notably, epileptic activity is related to progressive changes in functional organisation of the MTL (Bonora et al., 2011). Further, functional connectivity changes correlate with seizure duration, suggesting a direct association between seizure activity and functional connectivity (Wang et al., 2011). Therefore, changes in functional connectivity within specific networks during seizure activity may exert an influence on any pre-existing traits. In such a way, seizure activity may represent a symptomology similar to autistic traits, which is consistent with a more severe expression of specific neuronal connectivity patterns that integrate the triad of ASD impairments (Belmonte et al., 2004). It would be pertinent to investigate social skills in adults with epilepsy. In addition, a heightened attention-to-detail in TLE has been suggested but empirical evidence is lacking (Bear & Fedio, 1977). Communication difficulties, which are hindered by language impairments and language regression, are features of several epilepsy types (Schachter, et al., 2008, p.212; Tuchman, 2000). On the basis of such limited evidence, while some of these autistic characteristics may be present in adults with epilepsy, there is genuine uncertainty about whether all 5 subscales may be impaired.

5.1.2 Aim

This experiment aims to quantify the extent to which autistic characteristics are related to adults with epilepsy. It will employ the new method outlined in section 4.10, and the participants with epilepsy will self-report for two conditions: ‘without aura’ and ‘with aura’, and control participants will self-report for one condition. This research is useful for developing a better understanding of cognitive functioning during an epileptic event, and could be useful for developing an effective treatment plan for remediation.

Hypotheses

H1: There will be a difference in autistic traits between adults with and without epilepsy; adults with epilepsy will reveal increased autistic traits during the ‘without aura’ stage;

H2: There will be a difference in autistic traits for adults with epilepsy with and without seizure aura, with increased autistic traits during the seizure aura stage of epilepsy than without seizure aura;

H3: There will be a difference in autistic traits for adults with and without TLE, with increased autistic traits revealed by adults with TLE compared to other epilepsy types.

5.1.3 Method

5.1.3.1 Participants

This experiment recruited three groups: Group A: a control group of adults without epilepsy; Group B: adults with epilepsy with aura; Group C: adults with epilepsy without aura.

Method of Recruitment

Participants with epilepsy were recruited predominantly from two conferences held by a leading epilepsy charity. Email access was not a requirement. This experiment mainly used an event sampling method, and included:

Epilepsy charity conferences;

University of Bath [UoB] home webpage;

Adverts through University Psychology Departments.

Participants without epilepsy were recruited from students at the University of Bath where the research was conducted, or were known to the epilepsy participants, eg. an unrelated friend or partner.

Epilepsy Type

Participants were requested to self-report their epilepsy type at diagnosis: “What type of epilepsy do you have?” This self-reported epilepsy type was used for classification of participants. In the initial studies, participants were classified by primary type of epilepsy.

Exclusion criteria

Participants with epilepsy were excluded if they had a diagnosis of an ASD, or did not meet the criteria for active epilepsy (below). Participants without epilepsy were excluded if they had a diagnosis of an ASD, or any seizure disorder. Only adult participants ≥ 18 years were included. No participant throughout this research had an autism-epilepsy syndrome, eg. Dravet’s Syndrome.

Active Epilepsy

The literature review of research with adults with epilepsy revealed that although the term ‘active epilepsy’ is commonly used, it is rarely defined. Where it has been defined, criteria ranged from experiencing epilepsy within the last 6 months to the more conservative ILAE criteria of one or more epileptic seizures in the previous 5-year period (ILAE, 1993). Surgical outcomes are traditionally characterised using the Engel Class (Engel et al., 2003). However, as Jehi and colleagues point out, the Engel Classification is not entirely satisfactory, as Engel IC (free of disabling seizures for at least 2 years) and Engel ID (convulsions with AED discontinuation) also includes patients who never have a seizure after surgery (Jehi, Sarkis, Bingaman, Kotagal, & Najm, 2010). Jehi and colleagues highlight the discrepancy in the definition of the terms ‘seizure recurrence’ and ‘seizure-freedom’ after surgery (ibid., p.995). In addition, this thesis cannot support the term ‘disabling seizures’, as the investigation may reveal even mild seizure activity to be sufficiently psychologically disabling to warrant use of the term. Therefore the definition of active epilepsy in this thesis is taken from a conservative adaption of Engel IC:

Active epilepsy is defined as one or more seizure in the last 12 months (excluding seizure aura), or one or more non-aura seizure in the last 24 months and one or more seizure aura in the last 12 months, with or without AED discontinuation.

Participant Sample

The respondents comprised of 77 adults with epilepsy, 40 [52%] of these completed the AQ and met the experiment criteria for inclusion. This high dropout rate is discussed in section 5.1.5. Although the recruitment was aimed at adults with epilepsy with seizure auras, participants who responded who did not have seizure auras but met all other criteria were included to explore any group difference (see Table 5.1 and Table 5.2). The sample comprised $n=78$: Control Group $n=38$ [Female $n=27$,

Male $n=11$], Epilepsy with aura $n=32$ [Female $n=21$; Male $n=11$], Epilepsy without aura $n=8$ [Female $n=4$; Male $n=4$].

Table 5.1: Demographics

	Controls ($n=38$)			Epilepsy with aura ($n=32$)			Epilepsy without aura ($n=8$)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	42.1	(13.2)	22.4-70.9	40.8	(14.9)	19.3-71.2	40.4	(14.7)	20.3-62.2

Table 5.2: Classification of epilepsy type

Primary Type of Epilepsy	Group B	Group C	%
Temporal Lobe Epilepsy	10	2	30.0
Other Focal Epilepsy	5	0	12.5
Absence Epilepsy	4	1	12.5
Myoclonic Epilepsy	3	0	7.5
Idiopathic Generalised Epilepsy	0	4	10.0
Unknown	10	1	27.5
Total	32	8	100.0
TLE	10		31.25
No-TLE	12		37.50
Unknown	10		31.25

Epilepsy classification was self-reported by participants, primary epilepsy type at diagnosis was used for classification of epilepsy type.

Anti-Epileptic Drugs

Participants self-reported whether they were currently taking AEDs $n=36$, not taking AEDs $n=2$, or unknown, $n=2$. Participants were not required to rate whether they were receiving monotherapy: single AED intervention or polytherapy: multiple AED intervention, as this was not the aim of this research.

Epilepsy Onset

Participants were rated with: childhood-onset epilepsy <18 yrs $n=8$, or adult onset epilepsy ≥ 18 yrs $n=24$, or unknown, $n=10$.

Frequency

Participants reported their seizure frequency: Daily $n=6$, Weekly $n=10$, Monthly $n=10$, Yearly $n=12$, or Unknown $n=2$.

5.1.3.2 Materials

The Autism Spectrum Quotient (AQ) was provided in paper format and in digital format in Microsoft Office Word 2007. Participants without epilepsy were provided with: i) personal details form, ii) AQ and instructions iii) feedback form, iv) pre-paid addressed envelope. Participants with epilepsy were provided with: i) personal details form, ii) AQ (epilepsy-specific), and instructions, iii) an invitation to take part in further research, iv) feedback form, v) pre-paid addressed envelope.

The Autism Spectrum Quotient

The AQ is a structured questionnaire developed to assess autistic traits in adults with normal intelligence (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). It is a self-administered scale, shown to have good test-retest and interrater reliability. The AQ comprised of 50 short statements to assess 5 subscales which are reported to have reasonable construct validity (Baron-Cohen et al., 2001, p.6). The AQ was adapted to be epilepsy-specific so that it can be completed for the two conditions for each statement, however in keeping with The Autism Research Centre [ARC] recommendations, no wording was modified (Appendix A). The AQ and the AQ-adapted were accredited to ARC, with copyright mark in keeping with their guidelines of use.

Scoring

Participants self-rated their response on a 4-point Likert Scale: definitely agree, slightly agree, slightly disagree, or definitely disagree. Each statement scores 0 or 1. A score for an individual at high risk from an autism spectrum disorder tends to be high on the AQ, typically between 32 and 50, and the AQ has good discriminative validity and good screening properties at a threshold score of 26 (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). Participants with epilepsy are asked to rate whether their response decreases, stays the same, or increases in the ‘without aura’ condition. At the same time they are asked to rate their response when they are having an aura. Therefore, the ‘with aura’ condition is scored in relation to the ‘without aura’ condition, and scores are: decreases (-1), stays the same (0), increases (+1). The ‘with aura’ score can reduce, increase, or keep the original ‘without aura’ score, and provides an ‘effect’ measure for epileptic activity. The range of scores for ‘without aura’ is 0 to 50; the range for ‘with aura’ is -50 to 100.

Missing Data

The data revealed that all participants with epilepsy who omitted 3 or more responses in this study failed to complete the questionnaire. The omission of 3 or more responses occurred at the early stages of completing the AQ, within the first 10 questions. If ≥ 3 responses were left blank, their response was considered incomplete and the participants’ data was excluded. By comparison, this is less than other studies employing the AQ. For example, Hoekstra and colleagues used 5 omitted responses (10%, for one condition) for an exclusion threshold (Hoekstra, Bartels, Cath & Boomsma, 2008).

However, Experiment 1 differs from other experiments in that previous studies employing the AQ require 50 responses, whereas Experiment 1 requires 100 responses. Further, the epilepsy group have severe difficulties which may impact on their ability to undertake an assessment requiring 100 responses. It was anticipated that participants with epilepsy would have difficulties and a high dropout rate was expected. Participants with epilepsy who omitted ≥ 3 responses for this experiment failed to complete the AQ ($n=37$). Therefore the exclusion threshold was set at 3 omitted responses, which was most likely to result in failure to complete the questionnaire. Missing data values were replaced by the median value for each item. The high rate of missing data may be due to participants believing the task to be too difficult to undertake at the early stages of the AQ.

5.1.3.3 Design

The experiment was conducted as a mixed-design. The independent variable [IV] was group:

- i) Epilepsy, ii) no Epilepsy. The dependent variable [DV] was score, for one or two conditions:
- i) without seizure aura and ii) with seizure aura. Participants with epilepsy with aura could complete the AQ in two conditions: 'without aura' and 'with aura'. All other participants completed in one condition: 'without aura'.

5.1.3.4 Procedure

Participants who responded were invited to take part in a study investigating cognition and behaviour in adults with and without epilepsy. In addition to standard instructions, participants with epilepsy were instructed to complete the AQ for the 'with aura' condition: *"Please rate whether this decreases, stays the same, or increases during an Aura or part of the seizure which you can remember, by circling your answer in the right hand column marked WITH AURA."* An aura was defined as: "any symptom of epilepsy which becomes worse that is not part of the seizure, but can happen at any time. For some individuals it can indicate the start of their seizure." This definition was employed to help adults who may not realise that their aura can be epileptic. As the participants were invited to complete the questionnaire for both conditions, with and without aura, this required the participants to identify traits associated with their previous seizure auras, as well as traits without seizure auras. Participants were not expected to complete the AQ in one attempt, and were invited to complete the AQ in their own time.

5.1.3.5 Ethical considerations

This research was approved by the UoB Department Of Psychology Ethics Committee (UoB-Ethics), [ref: 08-526] which upholds the ethical standards of the British Psychological Society Code of Ethics for human research. The research aims were clearly communicated and there was no deception.

Participants were reassured about privacy, and the right to withdraw at any time for whatever reason, and without giving a reason. Participants were informed that all information collected during the research would be kept confidential and protected from unauthorised use or theft. Participants were not coerced into completing the task, and they were provided with contact details for access to support before, during or after their participation, and assured that all enquiries would be handled confidentially. The AQ is designed to avoid distress or threats to self-esteem. A feedback form was supplied to identify any unseen harm or discomfort, discuss any feelings that arose which may cause distress, to give feedback, or arrange for assistance if needed. Support was offered by the researcher. No evidence was obtained of a psychological problem sufficiently serious to warrant professional services. No medical, psychological or other unrelated advice was given, and no incentives were offered for participation.

5.1.3.6 Analyses

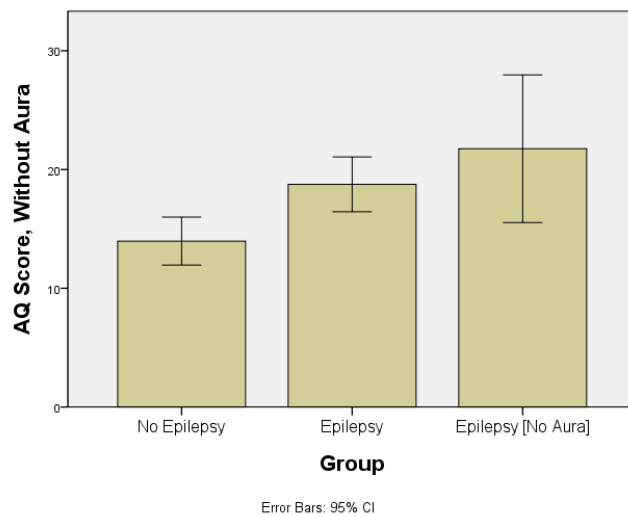
All analyses for Experiments 1-4 were carried out using Statistical Package for the Social Sciences (SPSS) version 14.2 and version 16.0. Significance level was set at a conventional level of 5% throughout the research project. As these studies are exploratory, trends approaching this level of significance will be reported: approaching significance = 0.051-0.99 significance. The reason is that to ignore any trends may exclude areas of importance.

5.1.4 Results

Group differences

Analysis explored group differences for score, without aura. Positively skewed data was corrected by square root transformation. Kolmogorov-Smirnov test was non-significant confirming normal distribution ($p > .05$), and Levene's test confirmed homogeneity of variance ($p = 0.66$). There was a significant difference between group ($F_{(2,75)} = 7.67$, $MSE = 5.11$, $p = .001$), see Figure 5.3.

Figure 5.3: AQ Score and SE for all Groups, without aura



Post-hoc analysis

Post-hoc analysis used pairwise comparisons controlling for Type 1 errors. Hochberg's GT2 method post-hoc test for small and unequal samples sizes was chosen, and Games-Howell procedure was additionally performed to confirm similar population variances (Field, 2005, p.341). Levene's test revealed homogeneity of variance ($p=0.66$). There was a significant difference between adults without epilepsy and adults with epilepsy with aura, $n=70$ ($p=.007$), there was a significant difference between adults without epilepsy and adults with epilepsy with no aura, $n=46$ ($p=.007$). However, there was no difference between adults with epilepsy regardless of aura, $n=40$ ($p=0.56$).

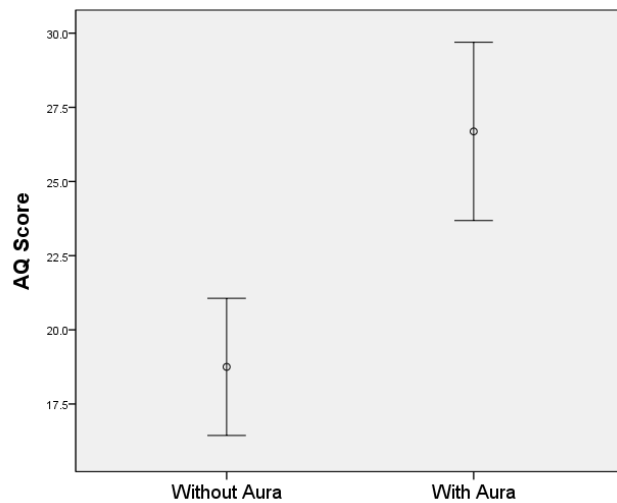
With/Without Epilepsy

Comparisons were made between adults without epilepsy and all adults with epilepsy [Groups B + C combined]. The Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p>.05$), and Levene's test confirmed homogeneity of variance ($p>.05$). The independent t-test showed a significant difference ($t=-3.71$, $df=76$, $p<.001$).

With/Without Aura

Analysis explored differences for score, between conditions, for adults with epilepsy with aura [Group B, $n=32$]. Data was positively skewed and this was corrected by square root transformation. The subsequent Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p>.05$). A paired-samples t -test revealed a significant increase during the 'with aura' condition ($t=-5.73$, $df=31$, $p<.001$), see Figure 5.4.

Figure 5.4: AQ mean scores and SE for Group B, with and without aura



Effect size

Analyses revealed a large effect size between conditions for group B (Cohen's $d=1.079$), and a medium effect size between groups A&B (Cohen's $d=0.768$).

Gender

Analysis for gender was conducted on all participants, as gender differences for autistic traits are also found in the general population. A two-way independent ANOVA with 2 factors, group [3 levels: A, B, and C] and gender [2 levels: M, F] explored the effect of gender in all participants on AQ score 'without aura'. The Kolmogorov-Smirnov test was non-significant revealing normal distribution for all groups ($p>.05$), and Levene's test revealed homogeneity of variance ($p=.88$). The main effect of group was significant ($F_{(2,72)}=7.60$, $MSE=5.14$, $p=.001$), there was no significant difference for gender ($F_{(1,72)}=.180$, $MSE=.267$, $p=0.61$, *n.s.*), and the interaction of group by gender was not significant ($F_{(2,72)}=.930$, $MSE=.626$, $p=0.40$, *n.s.*). Mean scores showed no trend in the direction of higher autistic traits in males. Mean scores for males and females with epilepsy during the 'without aura' condition were similar (males: mean=19.2; females: mean=20.2). Mean scores for males and females with epilepsy during the 'with aura' condition were also similar (males: mean=29.7; females: mean=30.3).

Further analysis of factors which may affect autistic traits are conducted only on Group B participants, adults with epilepsy with aura, as Group C participants are not the main focus of this investigation. Analysis will be conducted on the difference in score between conditions: 'with aura' score minus 'without aura' score termed 'aura effect score', as the effect of a seizure aura on autistic traits is the primary focus of this research.

Onset

Analysis explored differences for age at epilepsy onset (see section 5.1.3.1 for details) on the aura effect score. The Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p>.05$). Levene's test revealed homogeneity of variance ($p=.13$). An independent t -test revealed that there was no significant difference in score between onset groups ($t=-0.025$, $df=30$, $p=0.98$, *n.s.*).

Temporal Lobe Epilepsy

Analysis explored differences between TLE and non-TLE participants (see Table 5.2 for details) on the aura effect score. Data was normal and homogenous, as reported above. An independent t -test revealed that the TLE group mean score ($mean=11.3$) was higher than the non-TLE group mean score ($mean=6.2$), approaching a significant difference ($t=-1.38$, $df=20$, $p=0.091$ (*one way*) *n.s.*).

Frequency

Analysis explored differences for frequency of seizures (see section 5.1.3.1 for details) on the aura effect score. Data was normal and homogenous, as reported above. A one-way ANOVA revealed that there was no significant difference for frequency between group ($F_{(4,27)}=1.20$, $MSE=77.6$, $p=0.33$).

Epilepsy Type

Analysis explored differences for epilepsy type (see Table 5.2 for details) on the aura effect score. Data was normal and homogenous, as reported above. A one-way ANOVA revealed that there was no significant difference for epilepsy type between group ($F_{(4,27)}=1.85$, $MSE=58.2$, $p=0.50$).

Anti-Epileptic Drugs

No analysis was conducted due to small group sizes.

Subscales

Factor analysis was conducted to explore the factor structure of the AQ subscales based on the 5 domains of autistic traits developed by Baron-Cohen and colleagues (Baron-Cohen, et al., 2001). The aim of the factor analysis was to see if any factors correlated to reveal any specific subscales for the participants with epilepsy. The method of extraction for factor analysis was Principle Components, and 'Direct Oblimin' (with delta set at zero) performed the oblique rotation, since it is reasonable to assume that the subscales which measure aspects of autistic trait characteristics will be related (eg. Social Skills and Communication).

Table 5.5: AQ subscale descriptive statistics, adults with epilepsy

	Social Skills <i>mean (s.d.)</i>	Communication <i>mean (s.d.)</i>	Imagination <i>mean (s.d.)</i>	Attention switching <i>mean (s.d.)</i>	Attention-to-detail <i>mean (s.d.)</i>
<i>Without Aura</i>	2.59 (2.06)	3.22 (2.06)	3.06 (2.27)	5.41 (1.83)	4.41 (1.78)
<i>With Aura</i>	5.44 (2.88)	5.44 (2.71)	5.56 (2.21)	7.50 (3.13)	2.75 (2.59)

Factor analysis, 'without aura' condition

Factor analysis was conducted on Group B participants with epilepsy. Kaiser-Meyer-Olkin 'KMO Index' measure of sampling adequacy reveals adequacy for AQ subscales (KMO=0.587) and that the correlation matrix is suitable for factor analysis (Kaiser, 1970). Barlett's Test of Sphericity was significant, revealing that these variables are not independent of each other ($p < .001$). A manual check of the determinant value did not reveal multicollinearity in the data (determinant $> .00001$). However a manual check of the correlation coefficient table revealed multicollinearity in the data, and two factors were eliminated: 'Attention-to-detail' and 'Imagination'. Factor analysis was conducted on the remaining three factors to explore whether the remaining factors were highly correlated. The Kaiser-Meyer-Olkin revealed improved measures of sampling adequacy (KMO=0.659) rated 'mediocre' by Kaiser, and Barlett's Test of Sphericity remained highly significant suggesting that factor analysis is appropriate for the data ($p < .001$). Additionally, the KMO statistic for all individual variables are above the minimum value confirming all problematic variables had been eliminated (KMO $> .50$). A manual check of the correlation coefficient table and the determinant did not reveal singularity or multicollinearity in the data (determinant $> .00001$). All items had factor loadings over 0.4, and the domains 'Communication,' 'Social Skills' and 'Attention Switching' were highly correlated with correlations varied from $r=0.43$ to $r=0.67$. One component was extracted comprising of these three factors, suggesting these domains share common characteristics. This component revealed that 'Communication,' which has an eigenvalue of 2.07, accounted for 69% of the total variance. The two subsequent factors: 'Social Skills' (20%) and 'Attention Switching' (11%) account for smaller amounts of variance and both have eigenvalues under 1. Consequently, Kaiser's criterion of retaining component factors with eigenvalues greater than 1 determines that only 'Communication' is retained, and eigenvalues of the subsequent factors after rotation were not available. One reason may be that while the empirical basis for 'common rules' of sample sizes is unclear, data with a recommended sample sizes of over 100 participants may be more appropriate for this analysis (in Field, 2005, p.639). Table 5.6 shows eigenvalues and percentage of total variance explained by the factors before rotation.

Table 5.6: *AQ factors before rotation*

AQ	Factor 1 <i>Communication</i>	Factor 2 <i>Social Skills</i>	Factor 2 <i>Attention Switching</i>
Number of items (q's)	<i>n</i> =10	<i>n</i> =10	<i>n</i> =10
Eigenvalue	2.07	0.61	0.32
Communalities	0.77	0.74	0.56
% variance	69.0	20.2	10.7

This analysis is limited by three residuals (100%) with absolute values ranging from .061 to .207 which are greater than 0.05, and as this is more than the suggested 50% this highlights some grounds for concern with the reliability of this model for the analysis (Field, 2005, p.656). Therefore reliability analysis was conducted on the three subscales: Communication, Social Skills and Attention Switching. This analysis measured Cronbach's alpha, and the overall alpha value revealed good reliability of the subscales ($\alpha=.775$, $n=3$).

Factor analysis, 'with aura' condition

Kaiser-Meyer-Olkin revealed sampling adequacy for AQ subscales (KMO=0.545), and Barlett's Test of Sphericity was significant ($p < .001$). A manual check of the determinant value did not reveal multicollinearity in the data (determinant $> .00001$). However, a manual check of the correlation coefficient table revealed singularity in all 5 subscales in the data meaning that the IVs correlated too perfectly, therefore no factor analysis was conducted.

5.1.5 Discussion

This experiment explored autistic traits in adults with and without epilepsy. The null hypotheses H1 & H2 can be rejected, as adults with epilepsy score significantly higher than adults without epilepsy, and adults with epilepsy score significantly higher in the 'with aura' condition than 'without aura'. The null hypothesis H3 cannot be rejected and the experimental hypothesis H3 is rejected, as there was no significant difference in score for adults with and without TLE. However, there was a difference in mean score for the effect of the seizure aura, which was approaching significance. Further analysis revealed no effect for onset, gender or frequency. Factor analysis revealed a cluster of 3 subscales for the 'without aura' condition: Communication, Social Skills and Attention Switching. Factor analysis was not conducted for the 'with aura' condition, however the highest epilepsy group mean score in this condition is attention-switching, and the lowest mean is attention-to-detail. This indicates that difficulties with attention-switching increased again during a seizure aura, while a decrease in attention-to-detail occurred during a seizure aura, whereas the remaining subscales increased.

Table 5.5 which reports the group mean scores indicate very similar levels of difficulty reported for social skills, communication and imagination for each condition. The greatest change occurring between conditions is for attention-switching, which is unsurprising.

These results showed that all adults with epilepsy revealed higher autistic traits, even if they do not have seizure auras or TLE. However, those with TLE reveal a trend towards a higher score during seizure activity, which shows the advantage of analysing the ‘with aura’ condition separately.

Previous evidence suggests that TLE may be the result of a neuro-developmental disorder (Voets et al., 2011). One explanation for these findings may be that those with TLE may have more uncontrolled epilepsy. TLE is the most prevalent type of refractory epilepsy and patients with TLE often exhibit anti-epileptic drug resistance (Koyama & Ikegaya, 2005). Therefore if the AEDs were not as efficient in controlling the seizures, this may be revealed through the ‘with aura’ condition, and the score difference between conditions, but not the ‘without aura’ condition. Why AEDs are often ineffective in TLE is presently the subject of much investigation by pharmaceutical companies, but one reason may be due to the neurodevelopmental factors of TLE, which suggest a common neuro-developmental phenotype in which maldevelopment of the temporal lobes may be an important predisposing factor. However, to explore the effects of AEDs on autistic traits, further investigation is needed as AEDs were not accounted for in the analyses in this experiment. This lack of analyses was due to the small numbers of participants who were not taking AEDs. It is clear that another measure for AEDs is needed in this research project. An alternative explanation may be that the TLE group experience prolonged seizure auras and can recall them better.

There were no gender differences found in this experiment contrary to previous findings that control males score much higher than control females (Baron-Cohen et al., 2001). Among the AS/HFA group in Baron-Cohen and colleagues original study employing the AQ, there was no significant gender difference in score (ibid.). Therefore, while the adults with epilepsy have no diagnosis of any ASD and while the AQ is not a diagnostic tool for autistic traits, the results in Experiment 1 are consistent with these original findings (Baron-Cohen et al., 2001). There may be several explanations for the lack of gender differences in the epilepsy group. Firstly, males with epilepsy represented a small number of participants [$n=15$], which is nearly half as many as females with epilepsy [$n=25$]. Secondly, epilepsy has no sex boundaries affecting both males and females equally, and no significant gender differences in cognition or behaviour have been identified in individuals with epilepsy. However, males with early onset epilepsy do represent an especially vulnerable group. Consistent with this, consideration of gender is a factor for selecting AEDs. AED selection may therefore be another factor influencing autistic traits in this experiment. Gender specific factor analysis on the AQ

could highlight significant differences between males and females to exclude a male bias of any of the 50 statements within a subscale. In addition, further research to establish the influence of gender on autistic traits in adults with epilepsy would be valuable.

In the 'without aura' condition, 37.5% of females and 46.6% of males scored at the intermediate level (AQ score 20+), this compares with findings of adults with AS in which twice as many males scored at intermediate level than females (*ibid.*). It was found that, in the original study by Baron-Cohen and colleagues (2001), 79.3% of the AS/HFA adults scored 32 or above, and 2% of the control group scored 32 or above. In Experiment 1, only 9.3% of the epilepsy group and 2.6% of the control group scored 32 or above, however this increased to 25% in the 'with aura' condition for adults with epilepsy. These findings are far lower than 79.3% of adults with AS/HFA in the original study. However, no direct comparisons can be made between these scores as 95% of adults with epilepsy were reported taking AEDs which have been found to significantly reduce socio-emotional processing and are considered to significantly reduce autistic characteristics, whereas it is unknown how many adults with ASD were taking AEDs. This is important as AEDs would be expected to affect scores for the 'with aura' condition more than 'without aura' condition, and may have influenced the higher scores rather than the lower scores. Further, it would be expected that those who dropped out by not completing the questionnaire would have represented a more severely affected group of adults with epilepsy. Overall though, the results in Experiment 1 reveal less severe autistic traits compared with the AQ score ranges of adults with AS/HFA reported by Baron-Cohen and colleagues (2001).

The new method demonstrated that it was possible to quantitatively assess adults for the effects of epileptic activity. This method should increase validity and discrimination for what is being measured, as well as informing researchers about the psychological effects of epileptic activity. One effect of employing the new method is that AQ scores were adjusted in the second condition in response to the self-reported impact of epileptic seizure activity on autistic traits. If the epilepsy participant only experienced the autistic trait during seizure activity then they scored 1 per response; if the experienced the trait without seizure activity and this trait increased during seizure activity then they scored 2 per response. This increased the possible maximum score range from 50 to 100. However, if the participant did not experience the autistic trait without seizure activity they score 0, and if this trait decreased during seizure activity then they scored -1. Therefore the decreased scores would cancel any increased scores during the seizure aura condition, meaning that the adjusted AQ score would not be a false increase or inflated score. Of the 32 epilepsy participants who completed both conditions, 26 participants revealed an increase of autistic traits during the seizure aura condition, 1 participant revealed no change, and 5 participants revealed a small decrease in autistic traits of less than 3 points.

The highest increase in score was 28 and the greatest decrease was -3, revealing a wide range of scores for autistic traits in the seizure aura condition. Factors for this large variation were not found. However, AED control could be one possible line of inquiry for future research. Importantly though, this method yielded new findings and therefore may be useful for future research into the self-reported effects of epileptic activity.

In contrast with the evidence in Chapter 4, Experiment 1 revealed that autistic traits and childhood-onset of epilepsy were not significantly related which would be expected, although no comparisons were made for the TLE group and non-TLE groups separately. Individuals with infantile seizures often present with TLE later in life. Therefore, one explanation may be that as infantile seizures are often clinically invisible, missed diagnosis in early-life have resulted in adulthood diagnosis of epilepsy (Glykys et al., 2009). For some of the adult participants in this experiment however, onset of epilepsy was ‘acquired’ through a head injury, and a normal developmental period was assumed. Equally, it could be argued that not all adults with head injuries acquire epilepsy as a result, and it could be considered whether neuro-developmental factors increased the likelihood of epilepsy onset. This question of the contribution of neuro-developmental factors to autistic traits in adults with epilepsy requires further investigation. A broader phenotype of traits may suggest that adulthood-onset of epilepsy is not the only factor for these traits. Autistic traits are biologically pre-disposed, and while cause of epilepsy is unknown in 60% of adults, further enquiry into specific factors for acquired adulthood epilepsy to uncover a relationship with these traits would be valuable. However, this does not explain the significant increase of autistic traits during seizure aura and the decrease of autistic traits without seizure aura. This suggests a dynamic presentation of traits, according to epileptic activity, and that autism spectrum disorders and epileptic activity are more closely associated than revealed by previous psychological assessments. None of the participants had been diagnosed with any ASD, and it could be argued that these autistic characteristics have been previously unrecognised in these participants. This is consistent with the argument that autistic characteristics may be under-diagnosed in individuals with epilepsy (Clarke et al., 2005; Saemundsen et al., 2007; Steffenburg et al., 2003). That autistic traits are not well-recognised in adults with epilepsy may be the result of several reasons. Firstly, the increase in autistic traits during a seizure aura is consistent with suggestions that under-diagnosis may be due to the methodology employed (Clarke et al., 2005; Saemundsen et al., 2007; Steffenburg et al., 2003). Secondly, if these characteristics are commonly found in both ASD and epilepsy, this would be consistent with Steffenburg’s observation that autistic characteristics may be misinterpreted as epilepsy (Steffenburg et al., 2003). Finally, it has been suggested that AEDs mask some characteristics. However, the AQ is not a ‘diagnostic’ tool, and therefore although previously unrecognised autistic traits were identified, no participant reported

to suffer a clinical level of distress, so participants were not directed to seek professional assistance for autistic traits.

Of note, the lack of frequency effect suggests that in this experiment it may be that active epilepsy, especially in TLE, is related to higher autistic traits, rather than the frequency of the epileptic activity. This is surprising given that seizure frequency is known to result in structural damage due to the effects of repeated seizures (Aicardi, 1999). In this experiment, the group with ‘yearly’ seizures ranged having epilepsy between 1 year and 20+ years, and no differences were found in the group. Interestingly, one participant [#6] who reported ‘yearly’ seizures and also reported having had epilepsy for just one year, scored very high (46), in the ‘with aura’ condition, revealing the effects that were reported in the first seizure.

The high drop-out rate of 52% was disappointing, but expected. Adults with epilepsy were required to provide 100 responses, 50 for each condition. Each response required some reflection and consideration, and participants needed to compare a stage of epilepsy with their experience of being without epilepsy. This may be the first time the participants have been asked to make such comparisons explicitly. Recalling the memory of a seizure aura may have been tiring for the participant as it places a demand on memory processes. It may have equally been upsetting for the participants to self-report these difficulties. In addition, participants may already be physically and mentally exhausted with their epilepsy condition at the start of this process, and AEDs can cause a wide range of difficulties including fatigue. Generally, it was expected that this task would be difficult for participants with epilepsy to undertake, but the information provided by those who completed the AQ in both conditions is considered to be valid. However, further research is necessary to test the reliability of these findings. Additionally, the extent to which autistic traits are variable to epileptiform discharges without seizures in adults with epilepsy would be a valuable line of enquiry.

Given that adults with epilepsy score significantly higher for autistic traits than adults without, it would appear that even when there is no epileptic activity, significant differences can be detected. This is consistent with brain-imaging evidence of abnormal functional networks which have been detected in individuals with epilepsy even during the resting state (Zhang et al., 2011). During the ‘with aura’ condition, those with TLE revealed a trend towards increased autistic traits. Specifically, functional impairments in mTLE have been related to a disorder of neural networks (Zhang et al., 2009). As such, the evidence suggests that the presence of autistic traits may depend on how the epileptic networks interact with each other during a resting state, and that the patterns of autistic traits during the ‘with aura’ condition may reflect the specific networks affected by seizure aura activity.

Abnormal neural connectivity in ASD was first defined by Hughes (2007). Belmonte and colleagues state that network connectivity patterns on brain activation are consistent with the triad of impairments and the high co-morbidity of epilepsy in ASD (Belmonte et al., 2004). Structural abnormalities in the medial temporal lobe have been related to ASD, and the MTL has consistently been a brain region implicated in autistic traits (Salmond et al., 2005). However, a higher rate of autistic traits in all epilepsy types in the 'without aura' condition may suggest that it is not the origin of onset of epilepsy such as the MTL or the frequency of seizures that are related to autistic traits, but that having a brain specifically vulnerable to epileptic activity may increase the risk of autistic traits. Notably, epileptic activity is related to progressive changes in functional organisation of the MTL (Bonora et al., 2011). This suggests that epileptic activity has progressive negative consequences for autistic traits, and this indicates that active epilepsy may be partly causal in the severity of autistic traits in adults with epilepsy. This would suggest that adults with epilepsy where seizures are resolved would have less autistic traits; however it has been suggested that early onset epilepsy interferes with the developing brain for specific networks and these individuals are liable to have permanent ASD (Tuchman et al., 2010). Taken together, the evidence on viewing epilepsy as a neural network disorder suggests that the networks affected by the process by which the normal brain becomes epileptic maybe responsible for the autistic traits, and that the brain regions affected by epileptic seizures may increase or decrease according to epileptic activity. This is somewhat consistent with the finding that it is not location of tubers in tuberous sclerosis complex, but the active epilepsy, epileptiform discharges and early onset which predicts which individuals develop ASD (Bolton et al., 2002). Note though, that early onset was not found to be a factor in Experiment 1.

The results also suggest that for adults with active epilepsy, autistic traits are not stable, but variable according to epileptic activity. However, this variability may not necessarily be noticeable in the ecologically valid environment by those who come into contact with individuals with epilepsy. For example, adults with epilepsy may compensate for days with higher autistic traits by withdrawing from the social environment. Alternatively, merely having higher autistic traits may result in social isolation without any conscious compensatory strategy.

ASD is widely-held to be a stable disorder, yet the high co-morbidity of epilepsy challenges this concept. For example, approximately one third of individuals with ASD have epilepsy, and given the significant increase in autistic traits during epileptic activity, autistic traits would be expected to increase and decrease. Recent research suggests that there is an accumulative risk of epilepsy in adults with ASD, in which an increased prevalence of epilepsy to 58.5% was found in 345 adults with ASD (Parmeggiani et al., 2010). Therefore it must be questioned whether autistic traits are variable in

adults with ASD, both with and without epilepsy. In addition, given the significant effects of AEDs, how does pharmaceutical intervention impact on the score range for the AQ outlined by Baron-Cohen and colleagues in these adults, does it mask these autistic traits? This questions the validity of psychological assessments for adults with ASD with a later diagnosis of epilepsy, exactly what is being measured in these adults?

The co-occurrence of IEDs in epilepsy and ASD has recently been highlighted by Yasuhara (2010). Yasuhara identified higher rates of IEDs in a large sample of children with ASD [85.8%] than Baise-Zung and colleagues found in a follow-up study of males with childhood-onset epilepsy in which only 45.7% had EEG abnormalities (Baise-Zung et al., 2006; Yasuhara, 2010). The relationship between IEDs and severity of ASD has been demonstrated by both Yasuhara (2010) and Muñoz-Yunta and colleagues (2008), yet the significance of this distinction remains uncertain. Experiment 1 demonstrated an increase in autistic traits during the ‘with aura’ condition where the presence of epileptiform discharges should be assumed. However, although a direct relationship here may be suspected, interictal epileptiform discharges cannot be excluded from the ‘without aura’ condition. Consistent with this consideration, the autistic consequences of epileptiform discharges have been previously identified in children with LKS without observable epileptic seizures (Besag et al., 2008). Further, as these discharges were not measured, there is no evidence that autistic traits in adults with epilepsy can be directly attributed to epileptic discharges alone. Therefore the relationship of the occurrence of interictal epileptiform discharges to autistic traits has yet to be determined.

Importantly, it could be argued that perhaps during epileptic activity, all cognitive functioning is impaired, not just functioning related to autistic traits. Further research is needed to establish whether these traits are genuinely related to epileptic activity and epilepsy.

Limitations

The main limitation of this experiment was that some statements for the ‘with aura’ condition may not be appropriately applied to a temporary stage of epileptic activity, and this may have limited the sensitivity of the assessment. The AQ consists of statements about childhood, and whether adults with adulthood-onset of epilepsy were reporting about a normal developmental period is unknown. As such, the findings in ‘without aura’ condition for adulthood-onset epilepsy can be considered more conservative. Due to the wording of the AQ, the new method resulted in double negative and double positive statements, which caused confusion. This confusion was fed back to the researcher by participants on the feedback form. One way of resolving this may be to assess each condition separately. The AQ may not be appropriate for low IQ individuals, and IQ of the sample in this initial

study is unknown. However, the AQ assumes reading comprehension skills, which is indicated by completed responses to all the questions. This experiment was limited by the small sample, and these comparisons have low power. Males, recent-onset adults, and those not taking AEDs were under-represented. The sample was recruited from adults attending a conference, and may represent a more able and mobile adult group. This experiment would have benefited from a good measure for AEDs.

Summary

The results reveal that adults with epilepsy report increased autistic traits, which increase and decrease according to whether epileptic activity is active or not. There was no effect for onset, gender or frequency. Those with TLE were more likely to experience a trend towards higher autistic traits when compared to other epilepsy types in the ‘with aura’ condition, and it maybe that these adults are refractory to AEDs and more likely to have poorly controlled seizure auras. The effects of AEDs on autistic traits were not explored. Future research should include a scale for AED control. Future research could include the new method in other psychological assessment tools, but care must be taken to avoid confusing the epilepsy participants. Finally, further research needs to firmly establish whether all cognition and behaviour are significantly different during a seizure aura, not just autistic traits.

5.2 Experiment 2: Investigation of Systemizing and Empathising in Epilepsy Employing the Adult Eyes Task Revised and Intuitive Physics Test

5.2.1 Background

In order to exclude whether all cognition and behaviour is impaired during a seizure aura, this research needs to demonstrate that only autistic characteristics are found during a seizure aura by demonstrating that while some abilities are impaired, other abilities are retained in adults with epilepsy. One of several retained abilities in adults with ASD is systemizing. Systemizing is the drive to analyse or construct a system or variables in a system, and rules or laws that govern the behaviour of a system and enable prediction of how the system will behave (Baron-Cohen, 2002). Enhanced attention-to-detail is considered to be a criterion for systemizing in those with high autistic traits (Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003). The empathising-systemizing [ES] theory of autism is a robust theory which suggests that ASD are characterised by a deficit in empathising abilities and intact or enhanced systemizing abilities, which may be heritable (Lawson, Baron-Cohen, & Wheelwright, 2004). Males obtain higher systemizing than empathising scores, and higher systemizing scores than females, while females present the opposite profile.

Impaired social communication abilities in ASD are argued to be the result of an inability to perceive and respond to the affective expression of others. The word ‘empathy’ is a translation from a German term meaning to project yourself into what you observe. Specifically, it is argued that the ability to attend to the mental states of others is a well-accepted index of empathy, and by recognising facial emotional expressions, an individual can understand and respond appropriately to other people. Eye-gaze is a fundamental part of social cognition and is important for engaging joint attention in the human social environment, and research of individuals with ASD reveals that the eyes alone can contain sufficient information for detection of complex mental states (Baron-Cohen, Wheelwright & Jolliffe, 1997). While other research has found that individuals with ASD can either be impaired in facial emotion recognition or detect basic emotions in the whole face, Loveland and colleagues found that those with ASD were most impaired at recognising mental states from the eyes alone (Loveland, et al., 1997). This led to the development of the ‘Reading the Mind in the Eyes’ test, which tests the ability to discriminate emotions from expressions in the eyes (Baron-Cohen, 2002). This task is described as an advanced ToM test which underpins social cognition. Broader measures on basic emotional abilities employing the Empathy Quotient [EQ] of 25 females with AS suggest a more general impairment in identifying complex emotions (Baron-Cohen & Wheelwright, 2004). However, a more recent study found similar performance on measures of systemizing ability and measures of affective and cognitive aspects of empathy between males and females (Lai et al., 2011). In contrast to this, even though neuroimaging evidence suggests that those with ASD decode faces differently, some inconsistent findings of FER in ASD have been demonstrated. This problem, according to a review by Harms and colleagues, is that individuals with ASD may use compensatory techniques (Harms, Martin, & Wallace, 2010). Harms questions whether difficulty in gleaned emotional information from faces leads to a broader social interaction deficit, or whether reduced interest in social interaction contributes to a deficit in facial emotion processing (ibid.). Of note, a study of 61 adults with ASD demonstrated impaired ToM but comparable performance on the Adult Eyes test, and no correlation between the two tasks (Spek, Scholte, & Berckelaer-Onnes, 2010). Research now suggests that emotional empathy may be intact in adults with AS (Dziobek et al., 2008; Harms et al., 2010). Despite these contradictory findings, the E-S theory is well supported by studies which suggest high levels of foetal testosterone are related to higher systemizing abilities in relation to empathising abilities and increased autistic traits (Auyeung et al., 2009).

Circulating testosterone and systemizing

Disruption to endocrine function in epilepsy has been attributed to epileptiform discharges and AEDs (Bauer et al., 2000). Previous research has demonstrated that plasma levels of testosterone alter seizure susceptibility, and may be responsible for male vulnerability to seizures (Mejías-Aponte, Jimenez-Rivera, & Segarra, 2002). Importantly however, previous research identified testosterone as

pro-convulsive for both sexes, as it modulates seizure susceptibility (Reddy, 2004). This is important, as circulating testosterone has been consistently related to non-rotational components of mental rotation, which is underpinned by the male advantage in systemizing. Research by Brosnan and colleagues demonstrated that systemizing correlated with a proxy for circulating rather than prenatal testosterone in male and female adults in the general population (Brosnan, Daggar, & Collomosse, 2010). For males, higher levels of testosterone have been found to lower their seizure threshold and increase seizure frequency and severity (Jayashekara & Flanagan, 2010; Mejias-Aponte, Jimenez-Rivera, & Segarra, 2002). While free testosterone levels are found to be lower in males with epilepsy than males without epilepsy, AEDs and specific type of AED have been identified as significant influencing factors on these levels (Bauer et al., 2000; Isojärvi, Tauboll, & Herzog, 2005). Conversely, successful epilepsy surgery in TLE normalises testosterone levels in males, which have been attributed to reduction of interictal epileptic discharges (Bauer et al., 2000; Montouris & Morris, 2005; Bauer, Dierkes, Burr, Reuber, & Stoffel-Wagner, 2011). The relationship of atypical testosterone levels attributable to IEDs in ASD and has yet to be investigated.

Systemizing and Empathising abilities in Epilepsy

Evidence for systemizing abilities in adults with epilepsy is lacking. In comparison to the E-S theory, there is a lack of evidence that adults with epilepsy focus on systems or line up objects in a repetitive way, which is considered to signify strong systemizing abilities. For this kind of understanding, it is worthwhile examining the visuo-perceptual changes occurring at onset of seizure auras. Adults with seizure auras can experience visual disturbances as the somatosensory cortex is implicated in seizure auras (Santana et al., 2010). During the seizure aura, the visual environment changes from being a predictable and systematic environment to an unsystematic environment which may not conform to the relational systematic laws of physical properties. As such, perception of an unsystematic environment may act as an early warning system of seizure activity. Adults with epilepsy may be highly motivated to attenuate to such unsystematic visual stimuli, which may not conform to the relational systematic laws of physical properties in terms of distance, perspective, or gravity. In order to make sense and bring structure to the visually disturbed environment during seizure activity, the cognitive ability of systemizing would provide knowledge of how features within the environment should interact and relate to each other. This knowledge could compensate for the disruption of somatosensory and sensory visuo-perception during a seizure aura, and a systemizing advantage may enable configuration of how an incorrectly perceived environment can be navigated. Importantly though, it has been suggested that attention-to-detail in ASD may be a consequence of sensory hypersensitivity (Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009; Happé & Frith, 2006). Therefore, while attention-to-detail was found to be increased in adults with epilepsy when compared to adults without epilepsy, this enhanced ability was not maintained during the ‘with aura’

condition. Investigating systemizing during a seizure aura may be valuable in adults with epilepsy, as different epilepsy-specific underlying explanations could be explored.

There is a growing body of evidence that adults with epilepsy have impairments of FER, and adults with FLE are specifically impaired in the ability to perceive emotion from the eyes (Benuzzi et al., 2004; Farrant et al., 2005). Impairments of face emotion recognition in TLE are considered to be related to impairments in advanced tests of theory of mind reasoning, and related to early insult and right medial temporal structures (Meletti et al., 2009; Shaw et al., 2004). Interestingly, male gender has been related to both early-onset and right hemispheric epilepsy, as such, males represent a group especially vulnerable to FER impairment (Doherty et al., 2003). This is because early onset epilepsy favours the right hemisphere, and right amygdala damage reveals greater deficits in emotional processing in males than females with epilepsy (Tranel & Bechara, 2009). Of note, the amygdala can be implicated during epileptic activity, which may have consequences for empathising abilities during a seizure aura (Bertram, 2009).

Experiment 1 employed a self-assessment tool to assess for autistic traits, however, it is necessary to empirically assess for autistic traits in adults with epilepsy. Wheelwright and colleagues demonstrated that autistic traits in adults can be predicted from measures of empathising and systemizing abilities (Wheelwright et al., 2006). In addition, adults with ASD were found to score higher than a matched control group for systemizing abilities. It would be highly appropriate therefore to empirically measure empathising and systemizing abilities in adults with epilepsy. Having established an increase in autistic traits in the adult epilepsy group, it is necessary to show that *only* autistic traits are found in adults with epilepsy without epileptic activity, that not all abilities are impaired and that some abilities are retained. Additionally, it will be necessary to show that *only* autistic traits are found in the ‘with aura’ stage of epilepsy, and that epileptic activity during a seizure aura does not disrupt all cognitive functioning, resulting in a deficit on all psychological assessments for this stage. As empathising and systemizing tasks are empirical measures of autistic characteristics, adults with epilepsy will undertake these tasks without any epileptic activity, and also *during their seizure aura*.

Seizure auras

For some adults with epilepsy, undertaking these tasks will not be possible, as not all adults with epilepsy have seizure aura’s. Additionally, there will be some adults who have seizure aura’s, but their epileptic activity may be too quick to complete the tasks. For other adults, their seizure aura’s may be too severe and levels of consciousness may be compromised, and it would not be appropriate

for these participants to undertake these tasks. However, there may be some adults with epilepsy who judge that they are able to complete the tasks during a seizure aura, and this information would be useful. The participants feedback from Experiment 1 revealed that some adults with epilepsy had not known what a seizure aura was and had previously been unaware whether their changes consistent with a seizure aura were due to epileptic activity or not, especially when the seizure aura did not progress into a more severe seizure. Ultimately, it will be the participant who decides at what stage their seizure aura begins or ends, and therefore the relationship of their performance during the seizure aura stage of epileptic activity will be subjective to each participant's knowledge of their own epileptic activity. This may be a limitation of the study, as the seizure aura stage will not be empirically measured. However, even though this is subjective, the information would be valuable, not only for an understanding the effects of a seizure aura, but also as a demonstration of the abilities or lack of abilities of an adult with epilepsy during their seizure aura.

Experiment 2: Empathising-Systemizing

5.2.2 Aim

This experiment aims to explore systemizing and empathising abilities in adults with epilepsy with and without aura, and in adults without epilepsy. While some evidence shows impaired empathising abilities in adults with epilepsy, there are currently no studies exploring whether systemizing skills are retained, and the higher AQ scores would predict a decline in empathising and retained or increased systemizing ability. In this investigation, the first aim is to determine whether systemizing abilities are retained, or whether the higher AQ scores in Experiment 1 are related to an increase in systemizing ability. The second aim is to determine whether this ability is retained or increased at the expense of empathising abilities, which is considered to provide a partial explanation for a deficit of socio-emotional processing in ASD. Thirdly, given the increase in autistic traits during the seizure aura condition, adults with epilepsy will undertake these tasks *during their seizure aura*.

Experiment 2a investigates systemizing abilities, and **Experiment 2b** investigates empathising abilities. It will employ the Intuitive Physics Test (IP) and the Adult Eyes Task-Revised. This experiment aims to be the first to quantitatively measure systemizing abilities in adults with epilepsy. Given that enhanced attention-to-detail may be a criterion for systemizing, consistent with findings from Experiment 1, an increase in systemizing ability would be predicted in the 'without aura' condition. However, as attention-to-detail decreased during the 'with aura' stage, a decrease of systemizing would be predicted during the 'with aura' stage of epilepsy. Previous research findings of impaired empathising abilities in adults with some types of epilepsy suggest a relationship of empathising ability to a diagnosis of epilepsy. This may also suggest a relationship with epileptic

activity. Therefore, a decrease in empathising abilities would be predicted in adults with epilepsy during both conditions.

Hypotheses

H1: Adults with epilepsy will demonstrate an increase in systemizing ability in the ‘without aura’ condition compared to adults without epilepsy;

H2: Adults with epilepsy will demonstrate a decrease in systemizing abilities in the ‘with aura’ condition compared to the ‘without aura’ condition;

H3: Adults with epilepsy will demonstrate a decrease in empathising ability in the ‘without aura’ condition compared to adults without epilepsy;

H4: Adults with epilepsy will demonstrate a decrease in empathising ability in the ‘with aura’ condition compared to the ‘without aura’ condition;

5.2.3 Method

5.2.3.1 Participants

This Experiment recruited two groups: Group A: a control group of adults without epilepsy, and Group B: adults with epilepsy. Experiments 2a & 2b recruited 22 participants (Epilepsy $n=18$) who previously completed Study 1.

Method of Recruitment

Participants were recruited predominantly through response from previous participants to take part in further research. Email access was not a requirement.

Exclusion criteria

The exclusion criteria were identical to that used in Experiment 1 (section 5.1.3.1). Participants were re-checked to ensure that at time of testing they met the criteria for ‘active epilepsy’. Three participants with epilepsy were excluded: one had prior knowledge of the tests, one did not correctly follow the instructions, and one participant did not return Experiment 2b.

Participant Sample

The sample comprised $n=42$ adults: Control Group $n=23$ [Male $n=6$; Female $n=17$], and Epilepsy Group $n=19$: [Male $n=6$; Female $n=13$]. The epilepsy sample comprised of adults with and without aura: Epilepsy with aura $n=13$, Epilepsy without aura $n=6$ (see Table 5.7 and 5.8).

Table 5.7: Demographics

	Controls (n=23)			Epilepsy (n=19)		
	<i>Mean</i>	<i>SD</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>
Age	55.7	(26.8)	22.6-66.5	36.2	(11.2)	18.4-56.1

Table 5.8: Classification of epilepsy type

Primary Type of Epilepsy	n	%
Temporal Lobe Epilepsy	6	31.5
Frontal Lobe Epilepsy	2	10.5
Complex Partial Epilepsy	3	15.8
Juvenile Myoclonic Epilepsy	1	5.3
Other Focal Epilepsy	1	5.3
Myoclonic Epilepsy	1	5.3
Tonic-Clonic Epilepsy	5	26.3
Total	19	100.0

Epilepsy classification was self-reported by participants, primary epilepsy type at diagnosis was used for classification of epilepsy type.

5.2.3.2 Materials

Participants were provided with a paper-based version of the Intuitive Physics Test [IP] (Experiment 2a), and the Adult Eyes Task-Revised (Experiment 2b) (Appendix B). Both tasks were sent to control participants. Participants with epilepsy received 2 booklets, one per condition: each booklet contained half of the IP task and half of the Adult Eyes task. All participants received Experiments 2a & 2b, an introduction letter, instructions, a word definitions booklet, a feedback form, and an SAE.

The Intuitive Physics Test

This test was developed to assess the perception of physical causality and higher-level understanding of physical-causality, understanding how things work with respect to the properties of physical objects (Baron-Cohen, Wheelwright, Scahill, Lawson, & Spong, 2001). The test comprises of 20 questions with a multiple choice format with 4 options [A,B,C, or D], only one answer is correct.

The Adult Eyes Task-Revised

The Adult Eyes Task Revised [eyes task] was developed from The Reading the ‘Mind in the Eyes’ Task, to assess the ability to correctly recognise facial expressions of emotion from the eyes (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). It was revised in 2001 to account for ceiling effects found to limit the test and reduce sensitivity (Baron-Cohen, Wheelwright, Hill, et al., 2001, p.242). The task presents a series of photographs of the eyes region of faces. The stimuli comprised of black/white photographs of male/female actors, 36 presentations, one per A4 sheet, size 115mm x 45mm. There are 4 response options (forced-choice words) distributed at each corner of the stimuli.

Scoring

The IP test was scored by number of correctly identified solutions: 1 point equals a correct response; 0 point equals an incorrect response; total score range: 0-20. Time was recorded for the duration of the task, separately for each condition, in minutes and seconds. The eyes task was scored by number of correct identifications of target word responses, for each correctly identified emotion: 1 point equals a correctly identified emotion; 0 point equals an incorrectly identified emotion; total score range: 0-36.

Missing Data

There were no missing data value substitutions, however consistent with the previous study, >3 omitted missing responses were excluded, [$n=3$].

5.2.3.3 Design

Experiment 2a and Experiment 2b were conducted as a mixed-design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV was condition: i) without seizure aura and ii) with seizure aura. Participants with epilepsy with aura could complete the tasks in two conditions: ‘without aura’ and ‘with aura’. All other participants completed in one condition: ‘without aura’.

Counterbalancing

The order of conditions were counterbalanced to eliminate order effects, by allocating each participant with epilepsy to either Group A or Group B in alternative order, according the order of their response to participate.

5.2.3.4 Procedure

Existing participants who responded to the advert for Experiment 1 were invited by email to take part in a study investigating cognition and behaviour in epilepsy. Respondents were posted the materials. Standard instructions for both experiments were provided. The only amendment was that participants doing half the IP test were instructed to complete it in 5mins instead of 10mins. In addition, a post-it note placed on top of one of the two booklets reminded participants with epilepsy which booklet to complete first. Participants with Epilepsy completed the task under two conditions: ‘with aura’ and ‘without aura’. Participants were instructed to undertake the tasks either i) during an aura or ii) without an aura. Consistent with the feedback from Experiment 1 that some participants had previously been unaware whether their changes consistent with a seizure aura were due to epileptic activity or not, participants were instructed to undertake either ‘only’ during an aura or on a day with

lots of aura activity and epileptic activity that they were aware of throughout the day. This was to ensure that the participant was noticeably experiencing epileptic activity throughout the day, even if they were not sure whether it was a seizure aura or not according to their knowledge of epilepsy. Conversely, participants were instructed to undertake the tasks during ‘without aura’ stage when they were not having any epileptic activity or epilepsy during the day. This was to ensure that the participant was noticeably free of any epileptic activity.

Response rates

Response rates from both groups of participants were low: Control participants: 23 of 32 completed responses [71.9%]; Epilepsy participants: 19 of 63 completed responses [30.2%].

5.2.3.5 Ethical considerations

Ethical considerations were as outlined previously in Experiment 1, and participants were informed of the task aims (section 5.1.3.5). This research was approved by UoB-Ethics, [ref: 09-637]. This research differed from Experiment 1 as it required participants to undertake the task during a seizure aura. Participants chose when to complete the task and the ability of a participant to write or read while experiencing a mild seizure aura though difficult, does not physically endanger the participant, since writing is an everyday task that they may otherwise be undertaking in their own home. The participants were advised not to let the requirements of completing the task prevent them from making any preparations that they would normally undertake for an epileptic seizure.

5.2.4 Results

Experiment 2a: Intuitive Physics Test

Analysis explored group differences for score, ‘without aura’. Kolmogorov-Smirnov test was non-significant confirming normal distribution ($p > .05$), while Levene’s test revealed a lack of homogeneity ($p > .045$). An independent t-test revealed that there was no significant group difference for total score when equal variances were not assumed ($t = .254$, $df = 41$, $p = 0.80$, *n.s.*). An independent t-test explored group time differences. Data was positively skewed and this was corrected by square root transformation. The subsequent Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p > .05$). Levene’s test revealed homogeneity of variance ($p > .05$). There was no significant group difference for total time taken ($t = -.421$, $df = 41$, $p = 0.676$, *n.s.*).

With/Without Aura

Analysis explored group differences for score between conditions, for the participants who were able to undertake the task during a seizure aura, [$n=13$]. Kolmogorov-Smirnov test was non-significant confirming normal distribution ($p>.05$). A paired-samples t-test revealed that the mean score for the ‘with aura’ condition (mean=4.62, SD=2.40) was lower than for the ‘without aura’ condition (mean=6.31, SD=1.80), these differences were significant ($t=-2.41$, $df=12$, $p=0.033$), see Table 5.9.

Table 5.9: Mean Scores and Time, adults with and without epilepsy

	Controls ($n=23$)	Epilepsy ($n=19$)	Without aura ($n=6$)	With aura ($n=13$)
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Adult-Eyes, Score	27.22 (SD=3.15)	26.79 (SD=4.98)	13.92 (SD=2.99)	13.15 (SD=3.18)
Intuitive Physics Score	10.39 (SD=2.52)	11.16 (SD=3.29)	6.31 (SD=1.80)	4.62 (SD=2.40)
Intuitive Physics Time (secs.)	10.5 (SD=4.59)	11.00 (SD=4.44)		

Experiment 2b: Adult Eyes Task-Revised

Analysis explored group differences for score, ‘without aura’. The Kolmogorov-Smirnov test revealed that the data was negatively skewed, and homogeneity of variance was not assumed. Data was reversed and corrected by square root transformation. The subsequent Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p>.05$), and Levene’s test confirmed homogeneity of variance ($p>.05$). An independent t-test revealed that there was no significant difference between groups ($t=.188$, $df=41$, $p=0.85$, *n.s.*).

With/Without Aura

Analysis explored differences between conditions, [$n=13$]. The Kolmogorov-Smirnov test revealed that the data was negatively skewed. Data was reversed and corrected by square root transformation. The subsequent Kolmogorov-Smirnov test revealed non-normal distribution for ‘without aura’ condition ($p=.002$), and a non-parametric paired-samples test, the Wilcoxon signed-ranks test with ‘exact’ test option for small sample size was chosen. There was no difference in performance between conditions ($z=-0.87$, $p=.416$, *n.s.*).

No further exploration was undertaken, as the analysis undertaken did not reveal the pattern of autistic traits that was demonstrated in Experiment 1.

5.2.5 Discussion

This experiment explored performance on the adult eyes task and the IP test as measures of empathising and systemizing abilities in adults with and without epilepsy. It was predicted that individuals with epilepsy would demonstrate increased systemizing abilities and decreased empathising abilities. Importantly, these differences have been demonstrated in individuals with ASD. The results of the IP test show that there was no difference in systemizing in adults with and without epilepsy. The null hypothesis cannot be rejected, and the experimental hypothesis H1 is rejected. The second hypothesis predicted that adults with epilepsy would demonstrate a decrease in systemizing ability in the ‘with aura’ condition compared to the ‘without aura’ condition, and the results showed that systemizing ability had decreased during their seizure aura. Therefore the null hypothesis can be rejected, and the experimental hypothesis H2 is accepted. The results of the eyes task show that there is no difference between groups or between conditions. As the null hypotheses H3 and H4 cannot be rejected, and the experimental hypotheses H3 and H4 are rejected. No comparison was made of group performance differences for epilepsy type, frequency, or AEDs.

The aim of this experiment was to show that not all abilities are impaired, and that some abilities are retained in adults with epilepsy. It was demonstrated that adults with epilepsy have intact performance on the IP test during the ‘without aura’ condition, despite having significantly higher autistic traits. Despite this, decreased systemizing was demonstrated for the ‘with aura’ condition, revealing that systemizing abilities decreased significantly when compared to their performance during the ‘without aura’ condition. This is the first research study that has been conducted to quantitatively measure systemizing abilities in epilepsy. There are several possible explanations for the decrease found during the ‘with aura’ condition. Firstly, this study employed a new method of psychological assessment which differed from the self-reporting undertaken in Experiment 1 as the abilities of adults with epilepsy were measured during their seizure aura stage of epilepsy. It was necessary to show that *only* autistic traits are found in adults with epilepsy and that not all abilities are impaired. This was found, as empathising abilities were found to be *intact* during both conditions, and systemizing abilities were retained during the ‘without aura’ condition. Therefore, the higher score for autistic traits found in Experiment 1 was not the result of a general impairment.

However, there are several considerations which must be applied to these findings. Firstly, it may be that the IP test was more cognitively demanding than the Adult-Eyes Task, as it required more complex reading skills. Therefore these results may have been obtained due to the level of task demands. The decrease in systemising during epileptic activity, while consistent with lack of enhanced attention-to-detail in Experiment 1 during the ‘with aura’ condition, is not consistent with

evidence of other enhanced autistic traits during epileptic activity. However, these findings establish the extent to which autistic characteristics are associated with seizure auras. Intrinsically, it may be that some autistic characteristics worsen during a seizure aura while other characteristics do not, and this information is valuable with respect to the semiology of the epilepsy stages of seizure activity. This is important as systemising not a core ASD characteristic. The most valuable line of enquiry would be whether the triad of core characteristics are impaired while other abilities are retained, and Experiment 1 previously demonstrated that two core characteristics of ASD, social skills and communication, are impaired during seizure aura activity.

It was demonstrated that adults with epilepsy have intact empathising abilities both with and without epileptic activity, despite demonstrating significantly higher autistic traits which included the subscale of social skills, in Experiment 1. Research has previously demonstrated impaired performance on the Adult Eyes task in individuals with epilepsy, and has established factors such as the type of amygdala damage and age at onset of epilepsy which are implicated. This indicates a variability of empathising in individuals with epilepsy which would be consistent with the view of ASD as a spectrum of deficits. Generally though, the findings suggest a genuine difference in autistic traits in Experiment 1. Interestingly, this is somewhat consistent with previous research of adults with ASD who have demonstrated intact performance on the Adult Eyes task while also demonstrating a severe deficit of social skills (Spek et al., 2010). Empathising, although a crucial component of social cognition, is not a core ASD characteristic. Further, there is a lack of research of empathising abilities in adults with epilepsy. To date, no research has been conducted with broader measures of empathising and systemizing abilities employing other psychological assessment tools, and further research is needed to establish these abilities with a wider range of measures.

In Experiments 2a and 2b, only 6 adults with epilepsy in the sample were male, and previous research has demonstrated higher systemizing abilities and lower empathising abilities in males with ASD and in males from the general population with higher autistic traits. Consistent with this research, early-onset epilepsy can result in greater deficits of emotional processing in males than females (Tranel & Bechara, 2009). The intact empathising suggests that this is not impaired, however the female-bias sample may partly explain these findings. However, this would be inconsistent with more recent research which has demonstrated a deficit of basic emotional ability employing the Empathy Quotient [EQ] in ASD females (Lai et al., 2011). This recent study found no female or male difference in systemizing ability employing self-reported rather than empirical measures (*ibid.*). More importantly perhaps, intact empathising during epileptic activity is inconsistent with evidence that the amygdala is implicated during seizure activity (Bertram, 2009).

The increase in autistic traits in Experiment 1 was not the result of a more general impairment in abilities. However, scores from the ‘with aura’ condition suggests that adults with epilepsy have a significant increase in some of their autistic characteristics during epileptic activity, demonstrated through an increase for 4 of the 5 AQ subscales. This infers that epileptic activity is related to an increase in severity of some autistic characteristics in adults with epilepsy. However, further research is needed to establish the extent of these traits and characteristics. Although this does not imply causality for all epileptic activity causing autistic traits, the relationship of epileptic activity to autistic traits is important, and empirical measures are needed to establish the underlying mechanisms of this relationship and support these self-reported findings. Of note, the autistic traits which were not identified in Experiments 2a and 2b have also yielded mixed results in those with ASD. Systemizing is not consistently superior in ASD, and FER studies have yielded mixed results (Harms et al., 2010). Therefore, it would be difficult to argue that the results from Experiments 2a and 2b are inconsistent with studies of adults with ASD.

Nonetheless, it would be difficult to predict AQ measures from the results of measures of empathising and systemizing abilities in Experiments 2a and 2b. Wheelwright and colleagues demonstrated that AQ measures can be predicted from self-reported measures employing the EQ and SQ-R, and possible future research could replicate this study in adults with epilepsy (Wheelwright et al., 2006). This would be important as the researchers indicate that there may be important neurobiological links between strong systemizing and empathising, which implicates the number of autistic traits an individual possesses (ibid., p.52). Further, they may share a common biological mechanism such as foetal testosterone, which indicates that empathising and systemizing abilities may be heritable (Lawson, Baron-Cohen, & Wheelwright, 2004). Further research is needed to determine whether these abilities support or refute heritability of autistic traits in adults with epilepsy. One factor which was not controlled for were AEDs, which are known to impact on socio-emotional processing in those with ASDs (Hessen et al., 2006). Therefore, it is unknown whether AED intervention masked emotional processing difficulties in Experiments 2a and 2b in adults with epilepsy who have higher autistic traits.

Limitations

This research was limited by the poor response to the experiments, lack of male participants with epilepsy, and the effect of AEDs which were not accounted for. Further, the effect on scores as a result of mean age differences between the two groups is unknown. Future research could explore empathising and systemizing in adults with epilepsy employing the EQ and the SQ-R.

Summary

The results demonstrated that systemizing and empathising was intact in adults with epilepsy, and that empathising but not systemizing was intact during the seizure aura stage of epilepsy. This suggests that some abilities are retained with and without epileptic activity. Additionally, intact empathising and systemizing abilities were not consistent with the self-reported higher autistic traits in Experiment 1. Future research could specifically aim to measure performance of adults with epilepsy, and identify factors for performance such as gender, AED intervention, and age at onset of epilepsy.

Chapter 6

Autistic Characteristics

“*It is becoming clear that neuropsychological assessment during clinical audit needs to consider assessing socio-cognitive functioning in people with epilepsy.*”

*Dr. Jane McCagh (2009)
Liverpool Hope University*

6.1 Experiment 3: Social Responsiveness Scale, Shortened [SRS-S]

6.1.1 Background

Autism spectrum disorders are an early onset neurological condition which is characterised by a disruption of social interaction. Since Kanner’s original identification of the characteristics of autism, social impairments have been a central defining feature of ASD (Volkmar, 2011). The high rate of epilepsy in ASD has also been an early indicator that autism is a neurobiological disorder. Social cognitive functioning in epilepsy is likely to be influenced by neurobiological factors, however according to Hermann and Jacoby (2009), this contribution is currently poorly understood.

Importantly, the social impairments of ASD are detectable in very early childhood, and there is an assumption that the origins of autism may be due to an early disruption of neuronal development. Autistic-like traits are also found in the general population, which lacks a separation of clinical from non-clinical levels of difficulty (Happé et al., 2006). However, while epilepsy is a neurobiological disorder associated with developmental difficulties, it is not specifically characterised by heritability. Despite this, Experiment 1 identified significantly higher autistic traits in adults with epilepsy when compared with a sample of adults without epilepsy, and this was increased during their seizure aura. Experiment 2 demonstrated that not all abilities are impaired in adults with epilepsy, even during a seizure aura. This suggests that despite the lack of heritability or disruption of early neuronal development, the high co-morbidity and higher level of autistic traits may indicate a higher level of social impairments in adults with epilepsy. As such, there is a need to evaluate social impairments in adults with epilepsy, as they distinguish individuals with ASD and are central to its detection.

Epilepsy can have a negative impact on ‘psychosocial adjustment’ defined as: *‘the interaction between the individual and the social environment’*. Poor psychosocial adjustment has been associated with the social isolation and social stigma of having epilepsy. Where poor psychosocial adjustment has been identified, it has been found to occur more frequently in certain focal epilepsies such as TLE (Gois et al., 2011; Jokeit, 2010, p.582). As highlighted by Schacher and colleagues (2006), studies of advanced social cognition have not been extensively researched in epilepsy, and are therefore neglected. Aicardi states that despite the fact that social adjustment resulting from epilepsy can be unrecognised, it can be present in a significant number of individuals with epilepsy (Aicardi, 1999).

As Hennric Jokeit states:

“Comprehensive clinical studies have revealed that psychosocial maladjustment is a serious problem in many patients with chronic epilepsy. To what extent these maladjustments are caused by social burdens, stigma, and risk factors of active epilepsy, and to what extent they are due to dysfunctional social cognition, remains an open question,” (Jokeit, 2010).

Jokeit discusses why analysis of social cognition in adults with epilepsy is important:

“As acute difficulties in social cognition are not necessarily evident in brief interactions between physician and patient; and these symptoms are often subclinical in nature and, therefore, psychometrically difficult to ascertain, it is important to develop sensitive and standardized instruments to analyze social cognition in different modalities. Identifying deficits in social cognition would allow for the development [of] more specific treatment strategies aimed at improving social-cognitive abilities,” (ibid.).

Social cognitive abilities have received little attention in adults with epilepsy, even though social impairments are observed in children and found to be related to epilepsy type and frequency. Research of children with epilepsy with good cognitive development and without comorbidities have shown that they have similar adult educational outcomes to children without epilepsy, but have difficulties with social relationships (Chin et al., 2011). However, the lack of research in adults is surprising as the structures implicated in epilepsy onset are also important for social and emotional processing, and therefore advanced social cognition. However, there is some evidence that patients with MTLE and with left TLE reveal deficits in higher-order social cognition on tasks measuring social faux-pas (Kotaskova, Marusic, Kajukova, & Javurkova, 2010; Schacter et al., 2008). Interestingly, one study of 94 children with epilepsy found that an increase of parental social interactions significantly correlated with behavioural problems of their children (Pal, Das,

Chaudhury, & Sengupta, 2005). This research suggests that behavioural difficulties in epilepsy may originate from the interaction between their families' social environment. Early observations of the 'Autistic Artist' by Sacks (1985, p.214) reported how José, a speechless gifted autistic artist, initiated social interaction and began the rudiments of language when there was reduction of his epilepsy and improvement of EEG recordings. This well-known case reveals the possibility of improvement in social interaction where epilepsy is partly controlled. Recent evidence supporting such a possibility demonstrated that seizure-freedom during adolescence has been related to improvements of social functioning in adulthood (Lach et al., 2010). Together, this suggests that having epileptic activity may be related to social cognitive impairments, can be more severe in some epilepsy types, while seizure-freedom may be related to recovery of some functioning in the absence of 'active epilepsy'. In addition, research has demonstrated that chronic epilepsy may be a factor for social dysfunction; therefore it would be worthwhile investigating 'years of epilepsy' as a potential factor for severity (Jokeit, 2010; McCagh et al., 2009). If those with chronic epilepsy demonstrate worse social functioning, this may suggest an underlying accumulative effect of epileptic activity on autistic characteristics. Although the effect of AEDs on communication and socialisation in those with epilepsy is presently not well established, significant improvements have been found in those with ASDs (Di Martino & Tuchman, 2001). AED intervention may therefore either mask these difficulties in adults with epilepsy, or lead to seizure-freedom which may increase the likelihood of later improvements in social functioning.

The next experiment focuses on one single characteristic of social cognition. It aims to measure impairment in social interaction in adults with epilepsy by assessing reciprocal social interaction, which is highly related to ASD. This specific characteristic can be investigated by employing a shortened version of the Social Responsiveness Scale [SRS]. The SRS evaluates social functioning in children and adults, and is commonly used to screen for AS in children (Constantino et al., 2003; Rutter, Bailey, & Lord, 2003a). The SRS evaluates the ability to engage in emotionally appropriate reciprocal social interaction, which is considered a core characteristic of all ASD, and it measures the severity of autism spectrum symptoms. Reciprocal social behaviour requires the individual to identify and interpret the emotional cues of others appropriately, and to respond and engage in social interactions with others. Comparisons of the SRS and Social and Communication Disorders Check List have shown that the SRS is more suitable to screen for and identify specific autism traits, rather than unspecific social and communicative impairments (Bölte, Westerwald, Holtmann, Freitag, & Poustka, 2011). In addition, it distinguishes ASD from other psychiatric conditions, by identifying the presence and extent of the social impairment.

6.1.2 Aim

Autism spectrum disorders are characterised by impaired social interaction which are a defining feature of ASD. The literature review suggests that poor psychosocial adjustment is a serious problem for children and adults with epilepsy, and can be related to epilepsy type and frequency. Despite some evidence which demonstrates that impaired advanced social cognition has been identified in some epilepsy types, research of social difficulties and their underlying mechanisms have been neglected. While autistic-like traits are also found in the general population, the higher level of autistic traits in Experiment 1 may indicate that social impairments are related to having epilepsy and epileptic activity. Therefore, this experiment aims to investigate reciprocal social interactions in adults with epilepsy, as they are a specific characteristic of ASD which distinguishes individuals with ASD from those with an unspecific social impairment, and are therefore central to the detection of ASD characteristics. In this investigation, the first aim is to explore the extent to which impaired reciprocal social interactions are found in adults with epilepsy, which will determine whether the social components of the autistic traits identified in Experiment 1 are specifically related to ASD, or the result of more general social difficulties. The new method in Experiment 1 demonstrated that it was possible to quantitatively assess adults for the effects of epileptic activity. As this new method provided valuable information for this epileptic stage, the new method of assessing seizure auras will be adopted in Experiment 3. According to Fisher and Engel, some seizure auras are associated with an alteration of responsiveness (Fisher & Engel, 2010). Therefore, the second aim is to determine whether any impairments of reciprocal social interaction occur as a result of having epilepsy, specifically as a result of epileptic activity, or both. The literature review identified improvements in social interaction where epilepsy is partly controlled, where a reduction of epilepsy seizures and improvements of EEG recordings were identified. This is consistent with evidence of a relationship between remission of epileptic seizures and later improvements of social functioning in adulthood (Lach et al., 2010). Therefore, the third aim of this experiment is to determine whether there is a relationship between improvements of reciprocal social interaction which may occur as a result of remission of epileptic seizures. Experiment 3 will address this aim by including adults with epilepsy who no longer have epileptic seizures.

Brief Measures

Experiments 1 and 2 sustained low response rates and high rates of missing data, which may be due to participants believing the tasks were too difficult to undertake. As such, these Experiments yielded low numbers of participants with epilepsy. Therefore this research project would benefit from employing an abbreviated form of psychological assessments in these initial studies. Experiment 3 will employ a shortened version of the Social Responsiveness Scale [abbreviated in this thesis to the SRS-S], which is a brief, self-report assessment (Kanne, Christ, & Reiersen, 2009), see 6.1.3.1. Importantly, the researchers employing the SRS-S have demonstrated a significant positive

relationship between SRS-S and AQ scores (Kanne et al., 2009). Experiment 1 found that due to low numbers of participants currently not taking AEDs, analysis for the effects of AEDs on autistic traits was not possible. However, since the literature review suggests that AEDs may be a factor for improvements in some autistic characteristics in individuals with ASDs, this experiment will employ a self-rating AED measure of control of epilepsy using a 5-point Likert Scale. No further AED investigation will be conducted, as this is not the aim of this research.

Experiment 3 explores reciprocal social interaction, a specific characteristic of impaired social cognition in ASD, in adults with epilepsy: with and without seizure aura, and in adults without epilepsy. Consistent with previous research which has found social impairments in adults with epilepsy and given that higher autistic traits were found in adults with epilepsy, poorer reciprocal social interaction would be predicted in the ‘without aura’ condition in adults with epilepsy than adults without epilepsy. Consistent with previous research which has highlighted that the structures implicated in epilepsy onset for TLE, the most common type of epilepsy, are also important for social processing, and given that increased autistic traits were found during epileptic activity in Experiment 1, poorer reciprocal social interaction would be predicted in the ‘with aura’ condition compared with the ‘without aura’ condition in adults with epilepsy. Furthermore, consistent with evidence that improvements in social interaction have been found after a remission of epileptic seizures, poorer reciprocal social interaction would be predicted in the ‘without aura’ condition in adults who currently have active epilepsy compared with adults who no longer have active epileptic seizures, termed here as the ex-epilepsy adults. This prediction suggests that ex-epilepsy adults will demonstrate some improvements in social interaction after seizure remission. Finally, the relationship of AEDs to reciprocal social interaction will be explored, and consistent with some evidence that they mask difficulties in socio-emotional processing, a relationship between SRS-S score and AED control would be predicted in the ‘without aura’ and the ‘with aura’ conditions. This experiment aims to identify these impairments of reciprocal social interaction, and evaluate the extent to which they are related to autistic characteristics. This will provide a greater understanding of social functioning abilities in adults with epilepsy.

Hypotheses

H1: Participants with epilepsy will score higher than controls revealing poorer reciprocal social interaction during the ‘without aura’ condition;

H2: Participants with epilepsy will score higher in the ‘with aura’ condition than the ‘without aura’ condition, revealing a further decrease in reciprocal social interaction during a seizure aura;

H3: Participants with epilepsy will score higher than ex-epilepsy participants revealing poorer reciprocal social interaction during the ‘without aura’ condition;

H4: Participants with epilepsy with improved AED control will score lower than those with worse AED control, revealing a relationship between reciprocal social interaction and AED control.

6.1.3 Method

6.1.3.1 Participants

This Experiment recruited four groups: Group A: a control group of adults without epilepsy; Group B: adults with epilepsy with aura; Group C: adults with epilepsy without aura; Group D: ex-epilepsy adults. Criteria for Group D participants were included if they had a diagnosis of epilepsy but failed to meet the criteria for ‘active epilepsy’ defined previously in section 5.1.3.1. However, they were excluded if they had a co-morbid diagnosis of an ASD. Experiment 3 recruited 26 participants (Epilepsy $n=17$) who had previously taken part in one or more studies.

Method of Recruitment

Participants were recruited predominantly through response to adverts requesting adult volunteers with and without epilepsy (Appendix C). Email access was not a requirement. This experiment used an opportunity sampling method, and included:

Adverts on epilepsy charity websites;
Adverts through University psychology departments;
Recruitment of existing participants [Experiments 1&2].

Exclusion criteria

Exclusion criteria were identical to Experiment 1. Group D comprised of participants who met all other inclusion criteria for Groups B & C except ‘active epilepsy’ (see section 5.1.3.1).

Participant Sample

The sample comprised $n=106$: Control Group $n=19$ [Female $n=15$, Male $n=4$], Epilepsy with aura $n=58$ [Female $n=43$; Male $n=13$; Unknown $n=2$], Epilepsy without aura $n=18$ [Female $n=11$; Male $n=7$], Ex-Epilepsy $n=11$ [Female $n=4$; Male $n=6$; Unknown $n=1$], see Tables 6.1 and 6.2.

Table 6.1: Demographics

	Controls ($n=19$)			Epilepsy ($n=76$)			Ex-Epilepsy ($n=11$)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	42.5	(13.2)	22.6-66.4	36.0	(11.5)	18.2-60.9	37.3	(14.8)	19.7-63.6

Table 6.2: *Classification of epilepsy type*

Classification of epilepsy	<i>n</i>	%
<i>Primary Type:</i>		
Temporal Lobe Epilepsy	18	23.7
Other Focal Epilepsy	32	42.0
Absence Epilepsy	2	2.7
Myoclonic Epilepsy	2	2.7
Idiopathic Generalised Epilepsy	14	18.3
Unknown	8	10.5
Total	76	100.0

Epilepsy classification was self-reported by participants, primary epilepsy type at diagnosis was used for classification of epilepsy type.

Anti-Epileptic Drugs (AEDs)

This experiment will measure AEDs by employing a self-rating measure of the effectiveness of AEDs for controlling epilepsy, using a 5-point Likert Scale: 1=Totally uncontrolled, 2=Poorly controlled, 3=Partially controlled, 4=Reasonably well controlled, 5=Well controlled. Participants reported whether they were currently taking AEDs [$n=69$], not taking AEDs, [$n=2$] and unknown, [$n=5$]. Participants were not required to rate whether they were receiving monotherapy or polytherapy, as this was not the aim of this research.

Years of Epilepsy

To investigate whether chronic epilepsy may be a factor for poorer reciprocal social interaction, participants reported the total number of years of having epilepsy from onset. Onset of epilepsy was defined as date of diagnosis, as seizures before diagnosis would not have been necessarily epileptic. ‘Years of epilepsy’: $n=51$, [mean=19.6 years, SD=12.6, range: 1-52 years], or unknown, $n=25$.

Frequency

Participants reported their seizure frequency as: Daily $n=14$, Weekly $n=7$, Monthly $n=16$, Yearly $n=8$ and Unknown $n=31$.

6.1.3.2 Materials

Participants were provided with the experiment materials which comprised: i) personal details form, ii) The Social Responsiveness Scale-Shortened [SRS-S], iii) an invitation to take part in further research, iv) a feedback form. The SRS-S was accessed by participants on-line through ‘surveymonkey’ software (www.surveymonkey.com). An invitation letter, followed by a paper copy of the SRS-S, personal details form, and pre-paid addressed envelope, was posted to respondents without email access, $n=2$.

Shortened assessment

Unlike Experiment 1, Experiment 3 employs a shortened version of the well-validated full-scale assessment. The high drop-out rate of 52% in Experiment 1 illustrated the high-demand on the epilepsy participants of evaluation with a full-scale self-report assessment, possibly due to the effects of having active epilepsy and AED intervention. For these reasons, a shortened version of the full-scale assessment will be employed.

The Social Responsiveness Scale-Shortened

The SRS is a validated quantitative measure of severity of social impairment, and the full scale comprises of 65 items related to 5 domains of social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and mannerisms. SRS scores are highly heritable, generally unrelated to IQ, with high internal consistency and test-retest reliability (Constantino et al., 2003). The shortened version, the SRS-S, is a brief, self-report screening version, comprising of 11 items with the highest factor loadings (Appendix D). It includes items from each of the three DSM-IV autism domains of social impairment, language impairment and stereotyped, repetitive behaviours (Kanne et al., 2009). It is considered appropriate to investigate adults and has previously been employed to assess young adult students. Research employing this shortened version has found a significant positive relationship with AQ score (ibid.).

Scoring

Self-rated responses ranged from 1-4: 1 False, not at all; 2 Slightly true; 3 Mainly true, and, 4 Very true. The range of scores are 11-44. Epilepsy participants rated their statements twice (see 5.1.3.2).

Missing Data

Missing data values were obtained by using criteria identical to Experiment 1. For participants who had entered data twice, the most recent data was included for analysis, [$n=3$].

6.1.3.3 Design

The experiment was conducted as a mixed-design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV was score, for one or two conditions: i) without seizure aura and ii) with seizure aura. Participants with epilepsy with aura could complete the SRS-S in two conditions: ‘without aura’ and ‘with aura’. All other participants completed the SRS-S in one condition, ‘without aura’.

6.1.3.4 Procedure

Participants who responded to adverts were invited to take part in a study investigating cognition and behaviour in epilepsy. Respondents were posted the materials or sent an on-line link.

6.1.3.5 Ethical Considerations

Ethical considerations were identical to Experiment 1 (section 5.1.3.5). Additional considerations were made for on-line data collection. The research was approved by the UoB-Ethics, [ref: 09-674].

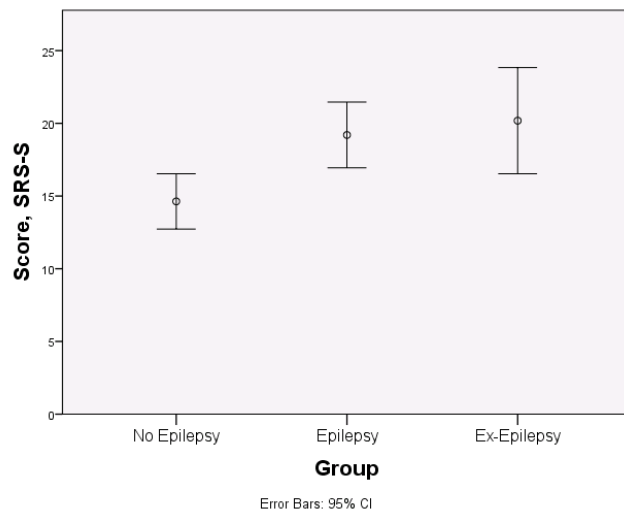
6.1.4 Results

Note: in this experiment, some participants completed the ‘with aura’ condition but did not complete the ‘without aura’ condition (see experiment limitations).

Without Aura

Analysis explored group differences for score, ‘without aura’: no epilepsy $n=19$; epilepsy $n=30$; ex-epilepsy $n=11$. Data was positively skewed and this was not correctable by square root or log transformation. Levene’s test confirmed homogeneity of variance ($p>.05$). The Kruskal-Wallis non-parametric ‘exact’ test for small samples was selected. As predicted, there was a significant difference for score between group ($H(df=2)=11.26, p=0.004$). Three non-parametric Mann-Whitney U tests (with ‘exact’ test for comparison with the ex-epilepsy group) were conducted to follow up this finding, and a Bonferroni correction was applied so that all effects are reported at 0.0167 level of significance. As predicted, this analysis revealed a significant difference between the adults with epilepsy ($mean=19.2, SD=6.1$) and adults without epilepsy ($mean=14.6, SD=3.9$) ($U=139.0, Z=-3.01, p=.003$) yielding a large effect size (Cohen’s $d=0.89$); a significant difference between the adults in the ex-epilepsy group ($mean=20.2, SD=5.4$) and adults without epilepsy ($U=43.5, Z=-2.65, p=.007$) yielding a large effect size (Cohen’s $d=1.19$); and there was no significant difference between the adults with epilepsy and the adults in the ex-epilepsy group ($U=141.0, Z=-0.71, p=0.50$), see Figure 6.3.

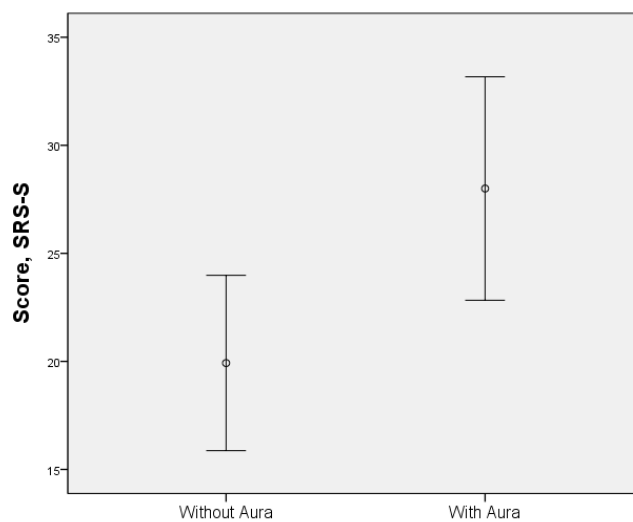
Figure 6.3: Mean scores and range by group on Social Responsiveness Scale



With/Without Aura

Analysis explored group differences between conditions, [$n=13$]. Data for ‘with aura’ condition was negatively skewed, and a non-parametric paired-samples test, the Wilcoxon signed-ranks test with ‘exact’ test option for small sample size was chosen. Participants with epilepsy scored significantly higher during the ‘with aura’ condition ($mean=28.0$, $SD=8.6$) than the ‘without aura’ condition ($mean=19.2$, $SD=6.7$), $z=-2.83$, $p=.005$, $r=-.55$, see Figure 6.4 below.

Figure 6.4: Error Bar Chart showing mean scores for ‘with aura’ and ‘without aura’ conditions



Gender

Despite no gender differences in Experiment 1, analysis for gender was conducted on all participants, as gender differences are a predominant feature related to autistic traits and characteristics in those with ASD and in the general population. A two-way independent ANOVA with 2 factors, [group, 2 x gender, 2] explored the effect of gender in all participants on SRS-S score ‘without aura’.

Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p > .05$), and Levene’s test confirmed homogeneity of variance ($p > .05$), for ‘without aura’ and ‘with aura’ conditions. The main effect of group was significant ($F_{(1,74)}=14.0$, $MSE=583.0$, $p=.001$), there was no significant difference for gender ($F_{(1,74)}=.001$, $MSE=.040$, $p=0.975$), and the interaction of group by gender was not significant ($F_{(1,74)}=.826$, $MSE=34.3$, $p=0.37$). Mean scores for control females were ($mean=14.37$) and epilepsy females ($mean=18.80$); for control males ($mean=13.00$) and epilepsy males ($mean=20.27$). Analysis will not be conducted on the ‘aura effect score’ due to the small number of participants who completed both conditions.

Anti-Epileptic Drugs [AEDs]

A Spearman’s rho was conducted to explore the relationship between AED control measured as ordinal data and SRS-S score. The analysis revealed a significant positive relationship for the ‘without aura’ condition $n=16$, $r=-0.43$, $p=0.048$ (one-tailed), and for the ‘with aura’ condition $n=58$, $r=-0.40$, $p=0.005$ (one-tailed), see Figure 6.5, note there are no error bars for the ‘without aura’ condition due to small group numbers.

Figure 6.5: i) Standard Bar Chart showing mean scores for AED control in ‘without aura’ condition;

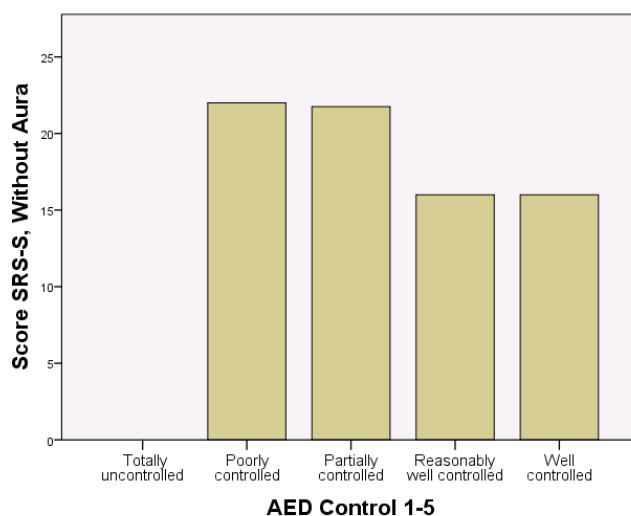
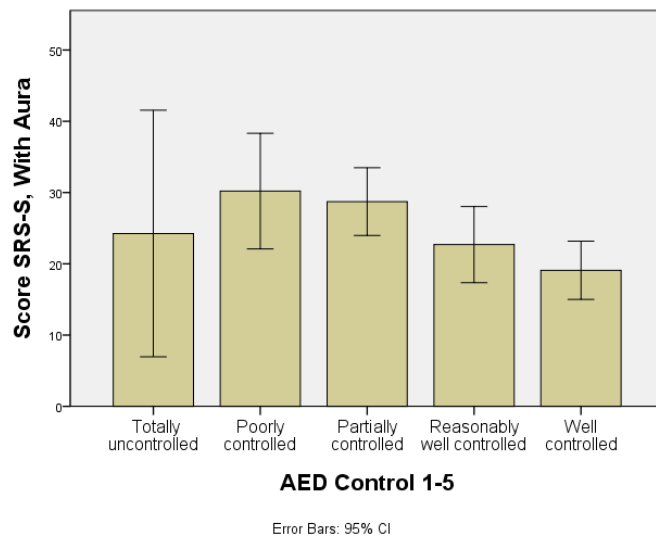


Figure 6.5: ii) Error Bar Chart showing mean scores with standard error scores for AED control in 'with aura' condition.



Years of Epilepsy

A Pearson's correlation coefficient explored the effect of 'years of epilepsy' on score, $n=51$. The analysis revealed a significant positive relationship for the 'without aura' condition $n=51$, $r=0.39$, $p=0.043$ (one-tailed), and a significant positive relationship for the 'with aura' condition $n=36$, $r=0.34$, $p=0.02$ (one-tailed), see Figures 6.6 and 6.7.

Figure 6.6: Score and 'years of epilepsy', 'without aura'

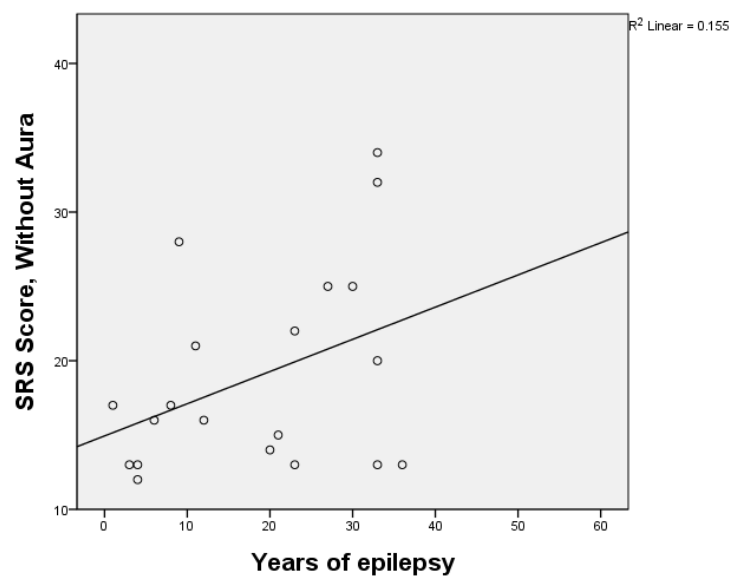
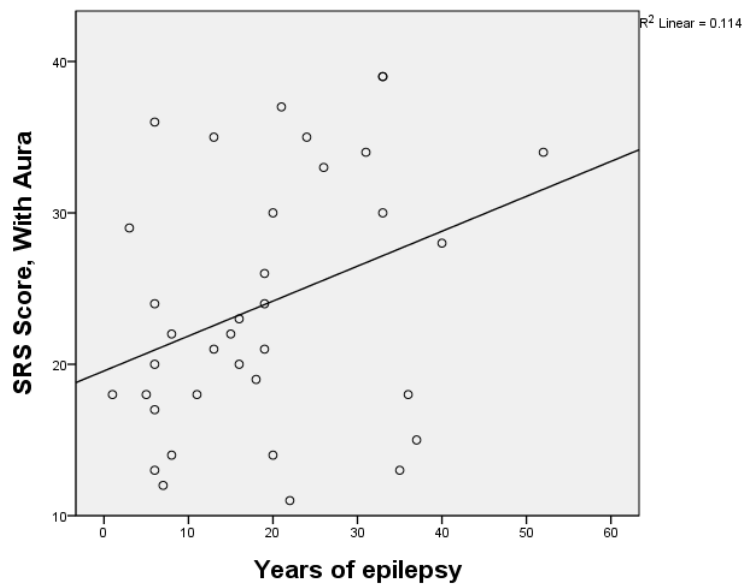


Figure 6.7: Score and ‘years of epilepsy’, ‘with aura’



Temporal Lobe Epilepsy

Analysis could not be conducted to explore differences between adults with TLE and non-TLE on the aura effect score, [TLE $n=4$, non-TLE $n=8$] due to small sample size.

Epilepsy Type and Frequency

No analysis was conducted for epilepsy type or frequency as no significant difference was found in Experiment 1. Further, as TLE is often refractory, only research of epilepsy type for untreated adults will demonstrate any genuine differences for epilepsy type.

Experimental Observations

It was observed that more epilepsy participants completed the ‘with aura’ condition without completing the ‘without aura’ condition, and it is unclear why this occurred. This may result in more conservative results for the ‘with aura’ analysis.

Multiple Regression

Multiple Regression was not conducted as a minimum sample size of 50 participants, with 8 participants per predicting factor, is suggested to generalise the results (Field, 2005, p.173). One limitation of lack of multiple regression is that it is presently unknown whether the independently analysed factors have a common underlying factor. For example, SRS score and ‘years of epilepsy’

analysis revealed a significant positive relationship, however it is unknown whether ‘years of epilepsy’ also correlated with AED effectiveness, which influenced SRS. To explore relationships between the factors influencing SRS score for underlying relationships, further research would be needed with a larger sample size.

6.1.5 Discussion

This experiment explored reciprocal social interaction in adults with and without epilepsy. The null hypotheses H1 & H2 can be rejected, as adults with epilepsy scored significantly higher than adults without epilepsy, and adults with epilepsy scored significantly higher in the ‘with aura’ than ‘without aura’ condition. The results show that there was no difference in reciprocal social interaction between adults with epilepsy and ex-epilepsy participants, therefore the null hypothesis H3 cannot be rejected, and the experimental hypothesis is rejected. Finally, it was predicted that adults with epilepsy with good AED control would demonstrate improved reciprocal social interaction compared to those with poor AED control, and the experimental hypothesis H4 is accepted as a relationship was found between AED control and SRS-S scores.

The significant factor for decreased reciprocal social interaction in the ‘without aura’ condition was years of epilepsy. Increased ‘years of epilepsy’ were related to higher scores, revealing a possible cumulative risk of severity of autistic characteristics from epilepsy onset increasing with age, possibly due to underlying accumulative effect of epileptic activity on autistic characteristics. In the ‘with aura’ condition, significant factors were: ‘years of epilepsy’, and AEDs. The results indicate that despite whether adults with epilepsy are having active or inactive seizures, they have significantly greater risk for decreased reciprocal social interaction than adults without epilepsy. This suggests that there is a strong relationship between social difficulties and having a diagnosis of epilepsy. This is consistent with Aicardi’s suggestions that social maladjustment can be present in a significant number of individuals with epilepsy (Aicardi, 1999). These findings are also consistent with Aicardi’s suggestion that these difficulties resulting from having epilepsy can often be unrecognised (*ibid.*). Importantly, in light of these findings, the full-item SRS could be used in future to screen for AS, as the sample of adults with epilepsy did not have a diagnosis of an ASD.

The increase in these difficulties during a seizure aura also implicates epileptic activity in having a possible role in disrupting normal social processes. This is consistent with the association between some seizure auras and an alteration of responsiveness (Fisher & Engel, 2010). While seizure auras may disrupt several cognitive processes, the self-reported decrease in reciprocal social interaction can be compared to intact empathising abilities demonstrated in Experiment 2. Despite the increase during

a seizure aura, adults without active epilepsy do not show the recovery pattern which would be expected. Therefore, these results reinforce the evidence suggesting that it is not only epileptic activity that is related to increased social difficulties, but that having epilepsy may predispose adults to poorer social reciprocity. Together, this supports the usefulness of employing a new method for psychological assessments which can provide valuable information that discriminate between epilepsy stages. This evidence is inconsistent with previous research which has shown some recovery of social difficulties in adulthood after remission of seizures in adolescence (Lach et al., 2010). However, it has not yet been determined how many years of seizure-freedom are related to a significant improvement, and the pattern of recovery from epilepsy in terms of social cognitive ability has not been well investigated. Further, definition of the term seizure-freedom is not without difficulties as previously highlighted by Jehi and colleagues (2010), see 5.1.3.1. Therefore, it may be useful to investigate whether ‘years of complete seizure-freedom’ correlates with a measure of improved reciprocal interaction.

The new method of assessing two conditions in this experiment yielded important information on the impact of AEDs. Results for the ‘with aura’ condition have revealed a significant effect in the expected direction, supporting previous evidence that AEDs can improve ‘socialisation’ (Di Martino & Tuchman, 2001). However, it is unknown whether participants with epilepsy attribute their own improved performance to the effectiveness of AEDs regardless of whether AEDs are actually contributing to improved performance. Generally though, these findings demonstrate that AEDs may be related to improved performance on measures of reciprocal social interaction, which suggests that AED intervention may help improve social difficulties in adults with epilepsy. However, this experiment employed a self-rated measure, and further empirical studies are needed to provide supporting evidence for a relationship of AEDs to reciprocal social interaction.

Previous evidence has suggested worse psychosocial adjustment in certain epilepsy types such as TLE and mTLE (Gois et al., 2011; Jokeit, 2010). However, Experiment 1 suggested that autistic traits were common to all adults with epilepsy and therefore not exclusive to any single epilepsy type. However, one possible explanation for previous findings of a higher trend in TLE may be that adults with TLE are regularly associated with anti-epileptic drug resistance (Koyama & Ikegaya, 2005). This explanation is partially supported by the experimental evidence suggesting that AED control is related to level of impaired reciprocal social interaction, which implicates AEDs in masking social difficulties in the non-refractory adults with epilepsy. An increase of ‘years of epilepsy’ were related to more severely impaired reciprocal social interaction, which is consistent with previous research showing that chronic epilepsy may be a factor for social dysfunction (Jokeit, 2010; McCagh et al.,

2009). This increase was found despite the underlying assumption that adults with chronic epilepsy were also taking AEDs for a greater number of years, and AEDs are significantly related to an improvement in socio-emotional processing. This suggests that the accumulative negative effect of epileptic activity on reciprocal social interaction is greater than the accumulative effect of AEDs on improving social functioning. Once more, gender was not found to be a significant factor for reciprocal social interaction. The literature review does suggest that males are vulnerable to a more severe presentation of epilepsy (Monte et al., 2007). However, gender differences in AED intervention may compensate to level these differences.

Research has shown that social reciprocal interaction measures on the full-scale SRS assessment are highly heritable (Constantino et al., 2003). While these results did not assess heritability, the relationship of higher SRS scores to having epilepsy which is generally not heritable, is inconsistent with evidence that autistic characteristics are highly heritable. Clearly, further research is required to assess the broader phenotype of autistic characteristics in adults with epilepsy. Autistic traits are also heritable in the general population, however evidence of a strong relationship between onset of epilepsy and autistic characteristics would raise further questions on whether some adults with autistic characteristics may be more prone to having epilepsy in later life. Generally, the results suggest that epilepsy is a condition with multiple factors which impact on the ability to interact socially. These factors include chronic epilepsy and AED control. Seizure auras may also be implicated in disrupting normal social cognitive processes. However epileptic activity alone cannot provide a comprehensive explanation for impaired reciprocal social interaction, especially as some adults have only yearly seizures. Adults with epilepsy are at an increased risk of social difficulties regardless of whether their epilepsy is active or what gender they are. This suggests that epilepsy may play a role in causality of social impairments that are autistic in their characteristics. However, this experiment employed a self-rated scale, and an alternative explanation may be that other psychosocial factors such as the stigma of epilepsy, negative effect on social relationships and the risk of having a seizure all impact upon social functioning, leading to a perceived loss of social interaction.

Sample

Participants with epilepsy were recruited from epilepsy charity conferences, adverts on charity websites and in Universities. Consistent with findings of children with epilepsy by Chin and colleagues (2011), the sample may reflect adults with good cognitive development and without comorbidities and those with poorer cognitive development and other co-morbid disorders may have been excluded by the recruitment method.

Limitations

The SRS evaluates the severity of social impairment, and is commonly used to screen for ASD. The shortened version only has 11 items, and some of these items may be difficult for participants to self-report if their seizure aura is brief. This experiment lacked participants who completed both conditions, and more took part in the 'with aura' condition than the 'without aura' condition, thereby limiting the power of analysis between conditions.

Summary

The results reveal that adults with epilepsy report severe social impairments which are masked by AEDs. The predominant risk factor is long-term epilepsy. Future research employing the full 65-items could explore which of the 5 domains reveal the most severe impairments in adults with epilepsy. Future research could examine whether there is a relationship between score and date of last seizure in an ex-epilepsy group, to improve understanding on whether these social difficulties resolve in adults who are long-term seizure-free. Future research could also examine relationships between factors with a larger sample of epilepsy participants.

6.2 Experiment 4: Restricted and Repetitive Behaviours in Epilepsy

6.2.1 Background

Having established that adults with epilepsy may be at higher risk for autistic traits and impairments in social interaction, this research project now explores another area of the diagnostic criteria of ASD: restricted, repetitive and stereotyped patterns of behaviour, interests and activities (RRB's). Research into RRB's has been limited, as they are not specific to autism. Even so, each of Kanner's original cases had manifested symptoms characterising the desire for sameness to a marked degree, and severity of autism has been correlated with 'sameness' behaviours (Campbell et al., 1990; Prior & Macmillan, 1973). Repetitive behaviours are a pervasive feature of autism, and severe deficits of flexibility and planning have been linked to executive functioning ability and a refractory hypothalamic-pituitary-adrenal (HPA) axis (Brosnan, Turner-Cobb, Munro-Naan, & Jessop, 2009; Happé, Booth, Charlton, & Hughes, 2006). These executive functioning impairments can distinguish those with AS from psychosis patients (Merchán-Naranjo et al., 2010). However, Happé and colleagues point out that there is not one cause of ASD, but that current cognitive accounts can be divided into those that posit a deficit in social cognition, and those that posit a deficit in the non-social processes (Happé et al., 2006). They argue that 'social' accounts such as ToM, emotion processing or social orienting do not provide a satisfactory explanation for repetitive behaviours, and therefore cannot plausibly account for difficulties in the non-social areas. Bodfish and colleagues were the first

to systematically study repetitive behaviours in ASD, designing a quantitative measure for a wide range of RRBs (Bodfish et al., 2000). Bodfish and colleagues assessed adults with developmental disabilities with and without autism, and revealed that the severity of repetitive behaviours also predicted the severity of autism and characterised the disorder. However, although part of the diagnostic criteria, RRB's have been found to be less severe among older individuals with ASD (Esbensen et al., 2009).

In epilepsy, classic teaching on the observation of epileptic seizures is that seizures are stereotypic events, which highly correlate with the seizure origin (Schacter et al., 2008, p.139). In a recent animal study, Kleen and colleagues demonstrated that animals exposed to the flurothyl model of early-life seizures showed *impaired behavioural flexibility* in later adulthood compared to controls (Kleen et al., 2011). These early-life seizures increased the thickness of the prefrontal cortex, and this thickness correlated with impaired behavioural flexibility. Interestingly, their brain tissue findings are consistent with the abnormal and increased brain growth that has been associated with *autism*. Their results suggest that the long-term consequences of early-life seizures extend beyond the hippocampus and also involve at least the prefrontal cortex. Therefore the researchers suggest that the frontal lobe structures may be permanently affected by seizures in early life, and that behavioural disorders in epilepsy may be related to these fixed alterations in the prefrontal cortex. All aspects of executive functioning such as flexibility and planning affect children with epilepsy, and are common across nearly all epilepsy syndromes (Høie et al., 2006). In adults with epilepsy, executive functioning deficits are found in those with TLE, with age at onset being the strongest factor (Schefft et al., 2008).

Research of restricted repetitive behaviours in epilepsy is lacking, and this is the first experiment to measure this core autistic characteristic. **Experiment 4** employs the Repetitive Behavior Scale-Revised (RBS-R) a quantitative measure of restricted, repetitive behaviours to assess with and without seizure aura stages of epilepsy.

6.2.2 Aim

This experiment aims to identify the difference between restricted and repetitive behaviours in adults with epilepsy: with and without seizure aura, and adults without epilepsy. There is good reason to suspect rigid behaviours and lack of flexibility in all epilepsies, and given that seizures are stereotypic, an increase during a seizure aura may be related to epileptic activity. Epileptic seizure events are considered to be stereotypic events, and AEDs reduce epileptic seizures. Therefore AEDs are implicated in the remission of stereotypic events. Further, this relationship suggests that there may

be some improvement in stereotypic behaviours after remission of active epilepsy. Although research evidence is lacking, the current evidence available focuses the experimental hypotheses as follows:

Hypotheses

H1: Participants with epilepsy will score higher than controls revealing increased restricted and repetitive behaviours during the ‘without aura’ condition;

H2: Participants with epilepsy will score higher in the ‘with aura’ condition than the ‘without aura’ condition, revealing a further increase in restricted and repetitive behaviours during a seizure aura;

H3: Participants with epilepsy will score higher than ex-epilepsy participants revealing increased restricted and repetitive behaviours during the ‘without aura’ condition;

H4: Participants with epilepsy with improved AED control will score lower than those with poorer AED control, revealing a relationship between for restricted and repetitive behaviours and AED control.

6.2.3 Method

6.2.3.1 Participants

This experiment recruited three groups: Group A: a control group of adults without epilepsy; Group B: adults with epilepsy; Group C: adults with inactive epilepsy [Ex-Epilepsy]. Experiment 4 recruited 68 participants (Epilepsy $n=40$; Ex-Epilepsy $n=11$; Controls $n=17$) who had previously taken part in one or more studies.

Recruitment

Method of recruitment, exclusion criteria and ex-epilepsy group criteria were identical to Experiment 3.

Participant Sample

The sample comprised $n=83$: Control Group $n=21$ [Female $n=18$, Male $n=3$], Epilepsy with aura $n=37$ [Female $n=30$; Male $n=7$], Epilepsy without aura $n=10$ [Female $n=6$; Male $n=4$], Ex-Epilepsy $n=15$ [Female $n=9$; Male $n=6$], see Tables 6.8 and 6.9.

Table 6.8: Demographics

	Controls ($n=21$)			Epilepsy ($n=47$)			Ex-Epilepsy ($n=15$)		
	<i>Mean</i>	<i>SD</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>
Age	41.2	(13.4)	23.0-67.0	38.4	(11.5)	22.0-62.0	37.3	(15.1)	19.0-64.0

Table 6.9: *Classification of epilepsy type*

Primary Type of epilepsy	<i>n</i>	%
Temporal Lobe Epilepsy	21	44.7
Other Focal Epilepsy	6	12.8
Myoclonic Epilepsy	1	2.1
Idiopathic Generalised Epilepsy	18	38.3
Unknown	1	2.1
Total	47	100.0

Epilepsy classification was self-reported by participants, primary epilepsy type at diagnosis was used for classification of epilepsy type.

6.2.3.2 Materials

The experiment materials comprised: i) personal details, ii) the Repetitive Behavior Scale-Revised (RBS-R), shortened version, iii) an invitation to take part in further research, iv) a feedback form. The RBS-R was accessed by participants on line through ‘surveymonkey’ software (www.surveymonkey.com). For the reasons outlined in section 6.1.3.2, Experiment 4 will adopt a shortened version of the full-scale assessment.

The Repetitive Behavior Scale-Revised

The RBS-R is a rating scale for measuring the presence and severity of restricted, repetitive behaviours, and designed to provide a quantitative, continuous measure of the full spectrum of repetitive behaviours (Bodfish et al., 2000). The RBS-R consists of 6 subscales: Stereotyped Behaviour, Self-injurious Behaviour, Compulsive Behaviour, Ritualistic Behaviour, Sameness Behaviour, and Restricted Behaviour. The RBS-R has high interrater reliability and internal consistency. The shortened version consists of 12 items related to the subscale ‘Sameness Behaviour’, measuring resistance to change and insistence on sameness (Appendix 6E).

Scoring

Participants self-rated their response on a 4-point Likert Scale ranging from 0-3: 0=behaviour does not occur, absent; 1=behaviour occurs and is a mild problem; 2=behaviour occurs and is a moderate problem; 3=behaviour occurs and is a severe problem. The range of scores is 0-36.

There were no missing data however, the most recent data was included for analysis for one participant who responded twice, [$n=1$].

Anti-Epileptic Drugs

Participants with active epilepsy self-reported either currently taking AEDs [$n=45$], or not taking AEDs [$n=2$]. Participants self-rated their AEDs using the same scale in Experiment 3.

6.2.3.3 Design

The experiment was conducted as a mixed-design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV was scored for one or two conditions: i) without seizure aura and ii) with seizure aura. Participants with epilepsy with aura could complete the RBS-R, shortened in two conditions: ‘without aura’ and ‘with aura’. All other participants completed in one condition: ‘without aura’.

6.2.3.4 Procedure

Participants who responded to adverts for Experiment 3 were invited by email to take part in a study investigating cognition and behaviour in epilepsy. Respondents were provided with the on-line link to the materials, and completed the task on-line.

6.2.3.5 Ethical Considerations

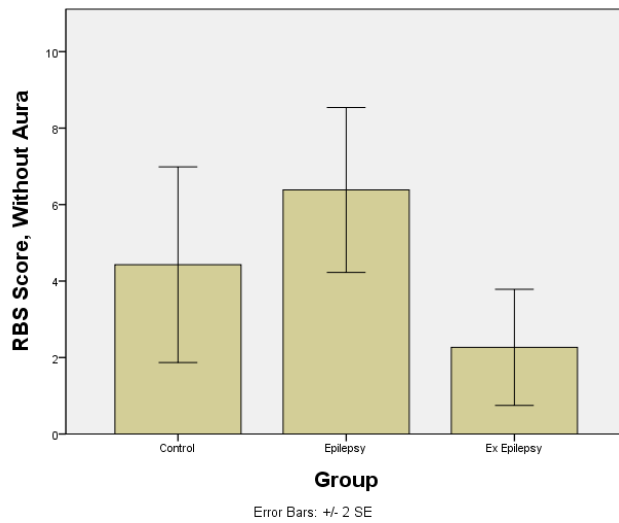
Ethical considerations were identical to Experiment 3 (section 6.1.3.5). This research was approved by the UoB-Ethics, [ref: 09-674].

6.2.4 Results

Group Differences

Analysis explored differences between participants with and without epilepsy in the ‘without aura’ condition. Kolmogorov-Smirnov test revealed that distribution was positively skewed which was not correctable by log or square root transformation. A non-parametric test, the Kruskal-Wallis non-parametric ‘exact’ test for small samples revealed there was a significant group difference in score ($H(df=83)=4.44, p=0.05$, *one way*). Three non-parametric Mann-Whitney U tests were conducted to follow up this finding, and a Bonferroni correction was applied so that all effects are reported at 0.0167 level of significance. Analysis revealed no significant difference between the adults in the ex-epilepsy group and adults without epilepsy ($U=136.0, Z=-0.72, p=.47$); no significant difference between adults with epilepsy and adults without epilepsy ($U=400.5, Z=-1.25, p=.211$); however there was a significant difference between the adults with epilepsy and the adults in the ex-epilepsy group ($U=234.5, Z=-1.97, p=0.049$) yielding a medium effect size (Cohen’s $d=0.73$), *see Figure 6.10 and Table 6.11*.

Figure 6.10: RBS-R total mean score and SE by Group



Within Group Differences

A paired-samples analysis explored score differences between ‘with aura’ and ‘without aura’ conditions, [$n=9$]. Kolmogorov-Smirnov test revealed normal distribution for scores ($p>.05$). There was no significant difference for score ($t=-0.964$, $df=8$, $p=0.36$, $n.s.$), see Table 6.11.

Table 6.11: Score by Group

		Score			
		Mean (SD)	Range	Effect Size*	Sig.
Controls $n=21$		4.43 (5.86)	0-16	0.29	$p=0.21$, $n.s.$
Epilepsy $n=47$	Without Aura	6.38 (7.39)	0-27	0.29	$p=0.21$, $n.s.$
	($n=9$) With Aura	7.89 (6.94)	0-17	0.21++	$p=0.36$, $n.s.$ ++
Ex-Epilepsy $n=15$	Without Aura	2.27 (2.94)	0-10	0.73+	$p=0.049$ +

* Cohen’s d

+ Between Epilepsy and Ex-Epilepsy Groups, B&C

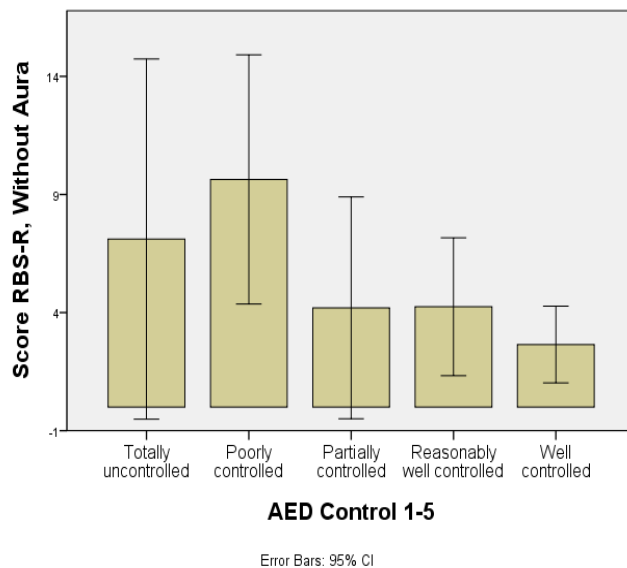
++ Between Conditions

As AED control and ‘years of epilepsy’ were found to be significant factors for Experiment 3, the following two analyses were conducted to investigate whether AEDs are related to RRBs.

Anti-Epileptic Drugs

Participants rated their AED control as: Totally uncontrolled, $n=5$; Poorly controlled, $n=11$; Partially controlled, $n=9$; Reasonably well controlled, $n=11$; and Well controlled, $n=9$. Two participants were not taking AEDs and therefore not included ($n=2$). A Spearman's rho was conducted to explore the relationship between AED control measured as ordinal data and RBS-R score. The analysis revealed a significant positive relationship in the direction predicted for the 'without aura' condition $n=45$, $r=-0.35$, $p=0.01$ (*one-tailed*), see Figure 6.12. No analysis was conducted on the 'with aura' condition due to the small sample size.

Figure 6.12: Error Bar Chart with standard error, for AED control and score 'without aura'



Years of Epilepsy

Analysis sought for a correlation in both conditions, exploring the relationship between score and 'years of epilepsy' since diagnosis, $n=47$. A Pearson's correlation coefficient revealed there was no difference for 'without aura' $r=-0.114$, $p=0.22$ (*one-tailed*) *n.s.*, or 'with aura', $r=0.323$, $p=0.20$ (*one-tailed*) *n.s.*

SRS-S Score

Pearson's correlation coefficient explored the relationship between social and repetitive behaviours for the 'without aura' condition, for participants who completed both Experiments 3 and 4, measured in SRS-S and RBS-R scores. A significant positive relationship was found for adults without epilepsy ($n=21$) $r=-0.56$, $p=0.022$ (*one-tailed*), and a significant positive relationship was found for the adults

with epilepsy ($n=13$) $r=-0.77$, $p=0.001$ (*one-tailed*). No analysis was conducted on the ex-epilepsy group ($n=5$).

No further analysis was conducted as there was no significant difference in scores between adults with and without epilepsy.

6.2.5 Discussion

This experiment explored restricted and repetitive behaviours in adults with and without epilepsy. The results show that there was no difference in restricted and repetitive behaviours between adults with epilepsy and the control participants, or between conditions in adults with epilepsy. The null hypotheses cannot be rejected, and the experimental hypotheses H1 and H2 are rejected. As predicted, there was a significant difference between adults with epilepsy with or without active epilepsy; therefore the null hypothesis H3 is rejected. This suggests that those without ‘active epilepsy’ have fewer RRB’s as they may recover from active epileptic stereotypy and repetitive behaviours. Further, a significant effect of AEDs was found upon restricted and repetitive behaviours in adults with epilepsy in the direction predicted revealing a relationship between for restricted and repetitive behaviours and AED control, therefore, the null hypothesis H4 is rejected. This may suggest that AEDs mask RRB’s, which could explain the lower score of the ex-epilepsy group. Consistent with this, all participants in the ex-epilepsy group were taking AEDs. There was no impact of chronic epilepsy and no other factors were analysed as the hypotheses H1 and H2 were rejected. RRB’s predict the severity of autistic traits, however a higher RRB score was not found in the epilepsy group who score higher on the AQ. This contradicts existing evidence of this relationship in those with ASD and in the general population, and may provide further evidence of the masking effects of AEDs. In Experiment 1, a new measure of AEDs were needed due to the lack of participants not undertaking AED intervention for comparison. Experiments 3&4 adopted a self-rating Likert scale, for rating AEDs. While this scale has resulted in some interesting correlations in these experiments, it should be remembered that as this is self-rated, it may also be a reflection of the participants’ well-being that is being attributed to the AEDs, but may also be the result of other unmeasured factors. However, as other studies have demonstrated AEDs improve social and emotional functioning, this would suggest that AEDs mask autistic characteristics in Experiment 3, and as AEDs improve ‘stereotypic events’ this would suggest that AEDs mask some but not all RRBs in Experiment 4. Together, this supports previous suggestions that AEDs mask autistic characteristics by Steffenburg and colleagues (Steffenburg et al., 2003).

The results revealed a strong correlation between RRB and SRS-S scores in adults with epilepsy, which suggest a relationship between social and non-social behaviours. This is inconsistent with Happé and colleagues suggestion that cognitive accounts of deficits can be divided into a deficit in social cognition and a deficit of non-social processes such as RRBs (Happé et al., 2006). However, further research is needed, as these are initial studies in adults with epilepsy which do not employ the full-scale items. The evidence suggests that RRBs could be related to whether epilepsy is active or inactive. Further analysis is needed to examine whether RRBs in epilepsy are related to remission of epilepsy, and to identify time points such as the adolescent period for when such remission is more likely to occur and when epilepsy is likely to re-occur across the lifespan of an adult with epilepsy. While Happé and colleagues argue that social accounts of ASD do not provide a satisfactory explanation for repetitive behaviours, only ‘epilepsy-specific’ accounts should be proposed to provide explanations for the relationship of RRBs and impaired reciprocal social interactions in adults with active epilepsy.

Limitations

The RBS-R evaluates the severity of rigid, repetitive behaviours, and only has 12 items. It could be argued that some participants may not be aware of their repetitive behaviours during the ‘with aura’ condition which may present as a symptom of the epileptic seizure itself. RRB’s may therefore be more difficult to distinguish than the social cognitive impairments in Experiment 3, resulting in some under-reporting of symptoms.

Summary

The results reveal a significant difference of the core autistic characteristic of restricted and repetitive behaviours between adults with epilepsy with, and without, active epileptic seizures. The adults with epilepsy who no longer have seizures self-reported fewer rigid and repetitive behaviours than those who currently have seizures. Although there was no difference between those who currently have seizures and the control participants, RRB’s may be masked by AEDs, which revealed a relationship in the expected direction. Future research employing the full 43-items may yield further data and reveal which of the 6 subscales reveal the most severe impairments in adults with epilepsy. Future research could examine differences in adults with epilepsy taking or not taking AEDs in the epilepsy and ex-epilepsy groups.

The initial Experiments 1-4 aimed to establish autistic characteristics in adults with epilepsy. The main findings from the initial experiments reveal that adults with epilepsy score higher for autistic traits than adults without epilepsy, and some of these autistic characteristics increase in severity

during seizure aura. The second experiment explored empathising and systemizing abilities. Results showed that adults with epilepsy were not impaired in inferring mental states from the eyes, suggesting that empathising skills are intact, and that systemizing skills were shown also to be intact in the ‘without aura’ stage of epilepsy, and decreased in the ‘with aura’ stage of epilepsy. Experiment 3 revealed impairments of a core characteristic of ASD, reciprocal social interaction, which were also present in the ex-epilepsy group, while Experiment 4 revealed that while recovery from epilepsy was related to improvements of rigid, repetitive behaviours, these non-social characteristics were not impaired in adults with epilepsy. The implications of these initial studies suggest that while some abilities such as empathising skills remain intact, autistic traits and characteristics are found to be more severe in adults with epilepsy than adults without epilepsy. Most of these characteristics share a relationship in severity to epileptic activity. In addition, there is a strong relationship between some of these characteristics and AEDs, which may mask their severity.

The theoretical implication of these findings will now be discussed in Chapter 7.

Chapter 7

Social Cognitive Functioning in Adults with Epilepsy

“Despite many years of speculation, it remains unclear to what extent psychosocial difficulties are related to the fact that patients are living with a chronic and stigmatising condition and to what extent they are related to neuropathology.”

Walpole, Isaac & Reynders (2008, p.1470)

7.1 Introduction

There is a paucity of research investigating autistic characteristics in epilepsy, and the first aim of this research project established the extent of these characteristics in adults with epilepsy with and without seizure auras. Despite significantly impaired reciprocal social interactions and significantly higher autistic traits, the adults with epilepsy were not different to adults without epilepsy in their rigid and repetitive behaviours. Happé and colleagues state that RRBs are not good markers of autism in the early years, and the researchers present considerable evidence for fractionation of the triad of impairments at the cognitive level which is consistent with fractionation at the genetic level (Happé et al., 2006). Notably, the researchers emphasise that the SRS is consistent with the notion of a broader autism phenotype, and does not show fractionation at the behavioural level. Taken together, this suggests that the SRS is a stronger indicator than measures of RRBs for autistic characteristics. They argue however, that researchers should abandon attempts to find a single cognitive explanation and focus on good accounts for each aspect of the triad. They state that non-social accounts of ASD struggle to explain the severity of social impairments in ASD. Consistent with this, a social cognitive account of autistic characteristics in adults with epilepsy would be most appropriate to provide a good account of social deficits as a single aspect of the triad. Further, a social cognitive account would address the initial results and the severity of social impairment that is consistent with autistic characteristics in adults with epilepsy.

The aim of this chapter is to explore the single key defining feature of autistic characteristics, social cognition, to address the findings in the initial research experiments. This chapter will then provide a detailed critical review of the current research of social cognitive functioning in individuals with epilepsy. The main research question asks: to what extent are the self-reported social difficulties in epilepsy related to social cognitive abilities? Pertinent theoretical models from the ASD literature will be discussed with focus on an elegant theory, the Somatic Marker Hypothesis, which demonstrates that emotions play a central role in social cognition and decision making, by providing an understanding of the neural systems of decision making. This hypothesis proposes that the formation of emotion-based biasing signals known as somatic signals must be intact to guide social interaction appropriately. The word somatic refers to the belief that people anticipate the ‘feelings of others’ by simulating those feelings within themselves with both positive and negative affect. Damasio terms the emotional signal as a soma, and the somatic state is the emotional change to the dynamic active changes within the somatic sensory structures (Damasio et al., 1996). A review of the present literature suggests that somatic marker formation in adults with epilepsy, as well as the mechanisms underpinning their formation, is currently unclear. Therefore, this theoretical model will be employed as a framework for investigating decision making abilities as a measure of somatic marker formation, in addition to evaluation of the mechanisms underpinning their formation. The findings will be considered in light of evidence of the significant social difficulties demonstrated in the initial experiments.

Social maladjustment in epilepsy

Psychosocial maladjustment, defined as extreme difficulty in dealing appropriately with other people, is a serious problem in individuals with chronic epilepsy (Jokeit, 2010). Factors associated with an increased risk of social dysfunction are severe and frequent seizures, chronic epilepsy, co-morbidity of other conditions, educational underachievement and early onset (McCagh et al., 2009; Rantanen et al., 2009). Experiment 3 showed a self-reported quantitative impairment in a core characteristic of ASD, reciprocal social interaction supporting findings of higher autistic traits in adults with epilepsy, which cannot be explained by existing research literature or by epilepsy type alone. There are two possible explanations for differences of social behaviour in adults with epilepsy. The first is that the psychosocial impact of epilepsy and the associated risks with potential dangers of having seizures is related to withdrawn and socially isolated behaviours. The second explanation is that the areas of the brain responsible for social cognition found to be functioning differently in those with ASD are also compromised in adults with epilepsy, regardless of epilepsy type. The contribution of the former has recently been debated, but research investigating evidence for the latter has been neglected.

Psychosocial difficulties in epilepsy

Historically, epilepsy is associated with significant psychosocial difficulties, and the social stigma of epilepsy has a negative effect on social identity, thought to cause social isolation (Jacoby, Snape, & Baker, 2005). According to McCagh (2009), quality of life [QOL] measures that explore the impact of epilepsy on social functioning are self-report methods which rely on the extent to which adults with epilepsy have insight into their social difficulties and may therefore be problematic. While measures demonstrate improvements in QOL after surgery, they do not adequately assess for improvements in social functioning. Further, as McCagh highlights, this is problematic for patients with RH lesions where a sense of self may be impaired (*ibid.*). However, while researchers of quality of social life studies highlight that the stigma of epilepsy persists long after seizure control, it is worth noting that seizure control does not imply seizure freedom. Indeed, the evidence demonstrates that QOL is strongly related to seizure control (Jacoby et al., 2005). This suggests a strong association between having seizures and having social difficulties. To feel stigmatised from a chronic illness or disability implies that the stigmatised individuals experience embarrassment and guilt. Such emotions are higher-order social emotions (Baron-Cohen et al., 1997). However, this contrasts with empirical evidence suggesting that epilepsy impairs advanced social cognition in mTLE, a common type of epilepsy, and as such these individuals may be deficit in processing higher-order emotions (Schacher et al., 2006). Consistent with this evidence, improvement in social outcome after epilepsy surgery have been reported, including improved social relationships and increased social interactions, in both children and adults (Hamiwka et al., 2011). Such evidence argues for neurobiological factors related to the genesis of epilepsy as a primary cause of social interaction difficulties. However, while it is argued that those with epilepsy have difficulties in social relationships, McCagh and colleagues state that it is hard to determine what facilitates this difficulty (McCagh et al., 2009). Importantly, the extent of social cognitive difficulties has not yet been established in a heterogeneous sample of adults with epilepsy. Therefore the main research question investigates a theoretical framework to explore the extent of these social cognitive difficulties.

Social cognitive difficulties in epilepsy

According to Schacher, research studies of advanced social cognition are neglected in those with epilepsy, even though temporo-limbic structures are important for social and emotional processing (Schacher et al., 2006). This is most surprising, given that animal studies have related TLE to functional changes in social behaviours that manifest as ASD, and consistent with such evidence, a number of studies have shown that those with TLE have worse social adjustment (Gois et al., 2011; Marin et al., 2008). On one hand, early onset is a consistent factor for impaired advanced social cognition (Shaw et al., 2004; Hlobil et al., 2008). Therefore it can be argued that adults with early

onset epilepsy may not have developed or may have impaired social abilities. Unfortunately, this cannot account for social functioning differences in adults who acquired epilepsy in adulthood, and have previously developed appropriate social skills. On the other hand, it could be argued that having epilepsy in adulthood would result in adults re-adapting their social lifestyle, due to difficulties with, for example, their 'epilepsy identity' (Jacoby, 2002). Equally though, the effect of seizure activity has been shown to impair social cognition, and consistent with this are findings that severity, frequency and chronic epilepsy increase the risk of social dysfunction in individuals with both childhood and adulthood-onset of epilepsy (McLaughlin et al., 2008; McCagh et al., 2009; Rantanen et al., 2009).

This research will now focus on theoretical models supported by empirical studies of social cognition, to explore a theoretical understanding of these initial findings.

7.2 Theoretical models of Social Cognition

Social cognition has been studied from various theoretical perspectives to understand how the self interacts and responds to the social environment. There are several theories of ASD focused on explaining deficits in social understanding. The Extreme Male Brain theory of autism proposes that those with ASD lack empathising abilities (Baron-Cohen, 2002). However, this theory is not supported by the research findings of Experiments 2a and 2b, and more recent evidence has shown that those with ASD are impaired in cognitive but not emotional empathy (Dziobek et al., 2008). The Amygdala Theory of Autism hypothesises that autism may be caused by an amygdala abnormality (Baron-Cohen et al., 2000). This is consistent with the presentation of TLE in a proportion of children with ASD. However, the theory is based on evidence that the amygdala is not activated in those with ASD when making mentalistic inferences from the eyes; therefore this theory is not supported by the research findings of Experiment 2b. Further, Dziobek and colleagues argue that their research indicates contrary evidence in those with AS (Dziobek, Fleck, Rogers, Wolf, & Convit, 2006). The two theories that are appropriate for consideration are the Theory of Mind [ToM] and the Somatic Marker Hypothesis [SMH]. The ToM hypothesises a primary deficit in social cognition, and while research in adults with epilepsy is lacking, ToM deficits have been linked to childhood-onset of epilepsy and to adults with FLE (Farrant et al., 2005). The SMH provides a neural explanation for how emotions regulate decision making under ambiguity which precedes explicit insight, through somatic states which guide social behaviour (Damasio et al., 1996). Recent research has demonstrated alterations in intrinsic functional connectivity within neural networks involved in emotional and interoceptive awareness in ASD (Ebisch et al., 2011). The researchers suggest that in light of the SMH and early theories of emotion, these functional abnormalities may be partly responsible for altered emotional experiences and impaired social abilities in ASD. Importantly, section 3.10

highlighted that the Theory of Neural Underconnectivity is a consistent feature within the high co-morbidity of epilepsy and ASD. Therefore the two primary theoretical models for consideration which will now be discussed are ToM and the SMH.

Theory of Mind

Successful social interaction requires recognition of another person's perspective, and requires ToM, discussed earlier in Chapter 3. This section will now discuss challenges with applying this theory. One of the most popular means of assessing ToM ability is the Adult Eyes Task-Revised, which assesses the ability to infer the mental states of others (Experiment 2). Results showed that adults with epilepsy did not differ from adults without epilepsy, indicating that the ability to infer the mental states of others was not impaired. Shaw observed a deficit in ToM tasks with early seizure onset compared to adults with epilepsy who acquired damage to a previously undamaged 'normal' amygdala in adult life and who did not show such impairments (Shaw et al., 2004). These findings have been replicated in individuals with mTLE and hippocampal sclerosis [HS], where impaired FER has also been associated with early onset of epilepsy (Hlobil, Rathore, Alexander, Sarma, & Radhakrishnan, 2008). This suggests that TLE may be related to impairment of ToM in cases of early onset with HS, however, in Experiment 1, there was no significant difference between those with TLE and those without, revealing severe social difficulties in most of the common epilepsy types. This supports earlier research proposing an overlap of TLE with JME, absence epilepsy, FLE, insular cortex epilepsy and tonic-clonic seizures (Devinsky & Najjar, 1999; Nguyen et al., 2009). However, the extent of such behavioural overlap is poorly defined, and the range of behavioural continuum has not been determined. Further, ToM is appropriate for assessing developmental disorders, and evidence shows that ToM is deficit in childhood-onset of epilepsy. Critically, there are theoretical challenges when applying ToM to an adulthood-onset population to assess developmental characteristics of ASD. ToM is related to amygdala damage, the amygdala can recover where there is remission of adulthood-onset. Additionally, Farrant and colleagues found clear impairments in FER performance and the Adult-Eyes task in adults with FLE but state that those with FLE do not exhibit a global impairment in social cognition, but exhibit specific difficulties (Farrant et al., 2005). Critically, the evidence in Experiment 3 found that social responsivity was significantly negatively affected compared to the control group; clearly, a theoretical framework other than ToM is needed to establish an explanation for the initial research findings.

7.3 Somatic Marker Hypothesis

Engagement in successful social interaction depends on representations of internal somatic states, as well as recognising and understanding representations of others. Damasio was the first to propose that

these somatic states have a major role in many aspects of social cognition. Central to the hypothesis are somatic markers, which are emotion-based biasing signals which respond to stimuli and can be measured by skin conductance response, [SCR]. The SMH proposes an explanation for how emotions regulate decision making through somatic states which guide social behaviour in complex situations (Damasio et al., 1996). This hypothesis was developed to address decision making deficits in patients with prefrontal damage, and central to the hypothesis is the assumption that damage to this region results in an inability to experience somatic states (Bechara, Damasio, Tranel, & Damasio, 2005). The researchers propose that SMH provide an explanation of how emotion influences decision making where a detailed cost-benefit analysis is not possible (Damasio, 1994; Damasio, Tranel, & Damasio, 1991). Such states guide responses for short and long term goals even if they are not experienced consciously, assuring that key goals are achieved according to the contingencies set by the social environment.

Integration of markers

Somatic markers may be created within the ventromedial cortex, and learned through an interaction between the amygdala and the hippocampus, and directly represented within the somatosensory cortices. The model of somatic marker formation assumes that they are integrated in the vmPFC. In addition to the implication of the vmPFC in the formation of somatic markers, recent evidence of lasting alterations resulting from early-life seizures has been found in an animal study (Kleen et al., 2011). The researchers found that repeated early-life seizures resulted in both structural changes in the PFC and abnormal PFC functioning. The structural changes identified were a thicker prelimbic PFC, and this change correlated with the measure of behavioural flexibility. It is well established that prefrontal cortex damage in adults with intact intellectual ability after normal development of social behaviour results in a severe impairment of decision making and a disruption to social behaviour (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). Consistent with this theory, damage to the ventromedial sector disrupts social behaviour profoundly, because while social cognition is preserved, patients with such damage fail to employ such knowledge resulting in atypical processing of emotion and feeling (Bechara & Damasio, 2000). This inability to process emotions results in a lack of engagement of complex social emotions, such as embarrassment, induced by specific social contexts (ibid). Prefrontal cortex damage can result in insensitivity to social cues, egocentrism, indifference to opinions of others, inappropriate affect and social withdrawal (Farrant et al., 2005). The researchers highlight that other intellectual abilities remain intact, although these patients are unable to learn as they lack the emotional component of this process (Bechara, Damasio, Damasio, & Lee, 1999; Damasio et al., 1996). Decision making is guided by emotion-biased somatic markers, and in support of the SMH, patients with vmPFC lesions demonstrate poor decision making and fail to generate anticipatory SCR's. Patients with vmPFC lesions also demonstrate an inability to reverse a previously learned contingency. Learning to reverse a contingency involves inhibition of the previously rewarded

response followed by a shift towards a newly rewarded response. Contrary to this, research has also demonstrated that vmPFC damage patients can be severely impaired in decision making but demonstrate intact performance on reversal learning tasks (Reimann & Bechara, 2010). However, impairment in either reversal learning or working memory can negatively influence decision making (ibid). While the medial frontal cortex has been associated with ToM, affective regulation, emotional processing and motivation, the vmPFC has been specifically associated with affective representations of self-referential processing. The vmPFC, Orbitofrontal, and Inferior lateral frontal cortex are associated with the representation and regulation of socio-emotional states (Abu-Akel & Shamay-Tsoory, 2011). Specifically, the vmPFC has been implicated in appropriate social behaviour, decision making, register of threat and fear extinction, social knowledge, emotional processing, memory, selecting and integration of sensory information, provides a flexible way of guiding activation, and is thought to generate social emotions, like compassion and empathy.

Assumptions

The SMH is based on three main assumptions: i) reasoning and decision making depend on conscious and unconscious operations, and overtly cognitive operations depend on sensory images from activity of early sensory cortices, ii) cognitive operations depend on support processes such as attention, working memory and emotion, and iii) reasoning and decision making depend on availability of knowledge about such situations. For the third assumption, the researchers describe the kinds of knowledge required, and include the knowledge of a) bio-regulatory processes, states, actions and emotion; b) facts, entities, actions, and action complexes; c) knowledge from linkages between the types of knowledge needed in a) and b); d) knowledge resulting in categorisation of items a-c (Bechara & Damasio, 2000, p.295).

7.3.1 IOWA Gambling task

To investigate the SMH in experimental laboratory conditions, Bechara, Damasio, Damasio and Anderson (1994) developed an experimental neuropsychological task, the IOWA Gambling Task [IGT]. According to Bechara and colleagues, in this decision making task the card decks simulate real-life decision making in terms of uncertainty for outcomes, as well as reward and punishments similar to real-life (ibid.). Research employing this task has provided key empirical support for the hypothesis that somatic markers significantly influence decision making behaviour under ambiguous circumstances preceding explicit insight. The IGT is constructed to present four decks of cards which either yield high immediate reward but a larger future loss over time, or conversely a lower immediate reward but a smaller future loss over time. These reward/punishment schedules are pre-programmed across 100 card selections so that two decks [A&B] are disadvantageous and two decks [C&D] are

advantageous across the task. Participants are unaware of which card decks are advantageous or disadvantageous, or how many cards they will need to select to complete the task. The aim is to decide which card deck selections will maximise the profit across the task. Participants can select from any deck at any time throughout the task. Mueller and colleagues highlight that the IGT simulates at least two separate processes crucial for complex real-life decision making: learning of probabilistic contingencies between stimuli and outcomes, and decision making based on this learning and a general motivational tendency to avoid punishment or approach reward (Mueller, Nguyen, Ray, & Borkovec, 2010). Successful IGT performance in healthy participants has been linked to generation of SCRs and intact somatic marker formation, compared to patients with vmPFC lesions who demonstrate impaired somatic marker formation and significantly poorer IGT performance.

7.3.2 Decision making in patients with epilepsy

Patients with temporal lobe epilepsy (TLE) usually present with unilateral temporal lobe structural damage comprising of the hippocampus, the parahippocampal gyrus, and usually but not always the amygdala (Labudda, Frigge, & Horstmann, 2009). However, even TLE patients without amygdala structural abnormalities may have functional abnormalities of the amygdala, and this may crucially affect the decision making processes. Labudda and colleagues demonstrated for the first time that patients with unilateral hippocampal damage in mTLE demonstrated disadvantageous decision making compared to healthy participants employing the IGT. Disadvantageous decision making occurred in patients with HS in the absence of any structural amygdala abnormalities, did not depend on side of seizure onset, and was not a consequence of epilepsy surgery (*ibid.*). Although the epilepsy group demonstrated disadvantageous decision making, this did not occur for every epilepsy patient. However, those patients with a preference for disadvantageous alternatives had earlier seizure onset. The researchers highlight evidence demonstrating the adverse effects of early seizure onset on neurodevelopment in the immature brain, and extend this to suggest that early seizures may increase the risk of decision making deficits. Patients with a preference for disadvantageous alternatives also performed poorer on some executive components, such as inhibition, cognitive flexibility and working memory. The researchers suggest that disadvantageous decision making in TLE patients may be due to an inability to learn the associations between the consequences of their deck selection and their probabilities, possibly due to a deterioration of continuous representations of the feedback from previous deck selections. Labudda and colleagues state that this assumption is consistent with previous studies demonstrating that working memory disturbances can cause disadvantageous feedback-based decision making. Generally, these results are unsurprising as the temporo-limbic structures implicated in the onset of epilepsy are important for social and emotional processing.

Of more importance is the demonstration of impaired decision making in patients without structural amygdala damage. According to the researchers, this may be due to the functional connectivity of the damaged hippocampus, as the close interaction between the amygdala and the hippocampus is important for emotion-based and feedback learning. The implication of such findings would be that hippocampal damage alone may impair decision making, through altered functional connectivity. This is important, as hippocampal damage is caused by seizures in temporal lobe epilepsy (Salmenperä, Kalviainen, Partanen, & Pitkänen, 1998). This suggests that epileptic seizures in TLE may cause decision making impairments which may have negative consequences for those with chronic TLE.

Based on these findings, Yamano and colleagues' aimed to further this investigation by exploring the contribution of the left and right temporo-limbic structures to decision making in right and left mTLE patients employing the IGT (Yamano, Akamatsu, Tsuji, Kobayakawa, & Kawamura, 2011). They found that right mTLE patients performed worse than left mTLE patients; however in this experiment, the contribution of the amygdala and hippocampus was not firmly established. Of note is that chronic epilepsy was related to worse scores for decision making. This is consistent with the possibility that epileptic seizures may have negative consequences for decision making abilities, as chronic epilepsy is associated with both amygdala damage and progressive hippocampal damage in intractable TLE, regardless of pathology (Adolphs, 2010; Mathern, Adelson, Cahan, & Leite, 2002). Taken together, these studies have implications for adults with epilepsy, as TLE is the most common focal epilepsy syndrome in adults, with focal epilepsy accounting for over 70% of all seizure activity (The Psychiatry Research Trust, 2011). Overall, there is a lack of research of decision making abilities in epilepsy, and where studies have been conducted the relative contribution of structures that underpin somatic marker formation have not been well established.

Many researchers consider the IGT to be heavily dependent on cognitive processes rather than emotional processes and that IQ maybe a confounding variable for performance on the IGT in non-healthy disordered populations. To examine the strength of such claims, Toplak and colleagues reviewed 43 studies to investigate the effect of cognitive functioning on IGT performance (Toplak, Sorge, Benoit, West, & Stanovich, 2010). Their review included 24 studies of measures of IQ, 15 studies for working memory, 18 studies for set-shifting as indices of executive functions [EFs], and 11 studies providing measures of inhibition. They found that only a small proportion of the studies reported a significant relationship between IGT performance and measures of intelligence, mostly with small to modest effect sizes, whereas the majority of studies reported no significant relationship. Where significant differences were found, there was also considerable variability in performance on

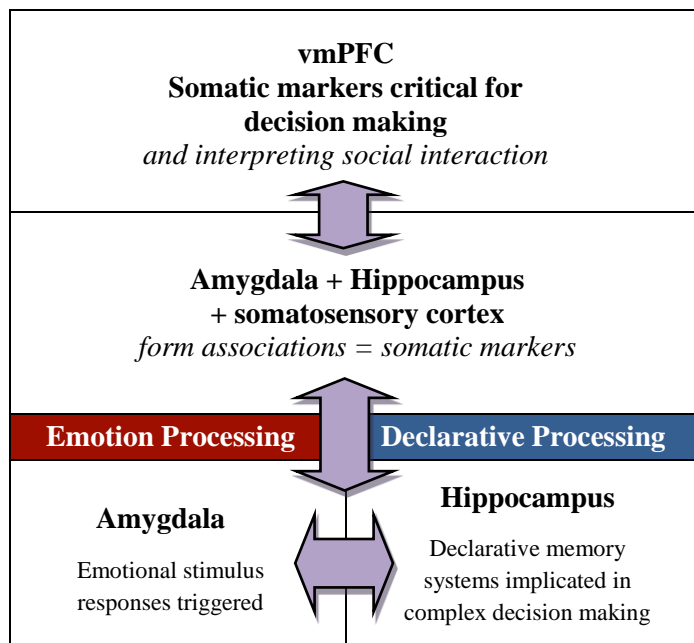
the IGT that was not captured by measures of executive functions or intelligence. Indeed, they concluded that it was likely that IQ and IGT performance were relatively dissociated processes, as indicated by “near zero correlations with IQ and EFs” (ibid., p.17). They also concluded that performance on the IGT is independent of working-memory capacity. Indeed, they concluded that overall, there is separability between decision-making on the IGT and cognitive abilities.

7.4 Anatomical structures implicated in somatic marker formation

Critical to understanding the SMH is the contribution of mechanisms which underpin the generation of somatic states. Research of decision making employing the IGT underpinning the SMH is exemplified through comparison of two rare cases of selective bilateral damage restricted to either the amygdala or the hippocampus, which revealed an amygdala-hippocampal double dissociation (Bechara et al., 1995). Evidence from such research has shown how bilateral amygdala damage compromises conditioned autonomic responses but spares the ability to acquire declarative facts, while conversely bilateral hippocampal damage compromises the ability to acquire declarative facts, but spares conditioned autonomic responses (ibid.). Unlike patients with bilateral amygdala damage, patients with vmPFC lesions are able to generate SCRs after a reward, but are unable to develop anticipatory SCRs before a selection.

Somatic markers are formed by combining information from the amygdala and hippocampus, and whilst there is debate on whether they are formed within or outside the vmPFC, the ventromedial prefrontal and sensory cortices, they have been consistently implicated in the generation and mapping of somatic markers (Figure 7.1). The ventromedial cortices have extensive bidirectional connections with the amygdala and hippocampus (Damasio et al., 1996). Neuroimaging studies implicate both the amygdala and hippocampus regions in reward-based learning, suggesting that the strength of the connection between these areas is essential for learning (Delazer, Zamarian, & Bonatti, 2010).

Figure 7.1 Brain structure hierarchy crucial for formation of somatic markers



In order to investigate the SMH, this research will also investigate the amygdala and hippocampus to find out what mechanisms that underpin the SMH may be related to decision making in adults with epilepsy. This investigation will be conducted with a focus on tasks of cognitive functioning that demonstrate a specific feature of ASD, as well as being specific to the formation of somatic markers. Previous studies have not firmly established the contribution of the amygdala and hippocampus to decision making abilities in epilepsy, however, according to Bechara and Damasio, these mechanisms may be inseparable (Bechara & Damasio, 2000).

7.4.1 Amygdala

Amygdala activation is critical for social learning and for socialisation (Davis, Johnstone, Mazzulla, Oler, & Whalen, 2010). The amygdala is implicated in the indirect consequences of experiencing emotional attributes of a situation where somatic states are evoked after winning or losing, and the enactment of somatic states when deliberating a decision that has future consequences. Adolphs states that the substantial literature now strongly suggests that the amygdalae, specifically the amygdalae neurons, have an important role in the response to both rewarding and punishing stimuli (Adolphs, 2010). Adolphs also highlights that some but not all studies suggest that the amygdala continuously codes updated representations of a stimulus value. Taken together, he argues that this dynamic continuous updating and coding plays a key role in social behaviour with respect to keeping track of the emotional or social value of the stimuli and to continuously update these changing social values

across time. This is of interest because the amygdala is well-known to be extremely susceptible to epileptic kindling, and is implicated in the semiology of TLE (Kullmann, 2011). For example, impaired functioning of the amygdala is implicated with early onset epilepsy, while amygdaloid damage is found in up to 60% of patients with intractable TLE (eg. Golouboff, 2008; Salmenperä, Kalviainen, Partanen, & Pitkanen, 2001). Early onset epilepsy favours the right hemisphere if onset is before 5 years of age, and right amygdala damage reveals greater deficits in regard to social-emotional processing and decision making in males than females (Tranel & Bechara, 2009). Chronic epilepsy is associated with a more severe presentation of social and emotional functioning, and can result in medial temporal sclerosis if severe and untreated (Adolphs, 2010). However, the evidence for FER deficits is less clear and some studies fail to find significant FER deficits in patients with epilepsy and unilateral amygdala damage (Adolphs, Tranel, Damasio, & Damasio, 1994). While amygdala functioning can recover in adults, it may be that chronic epilepsy prevents this recovery. Additionally, AEDs significantly improve socio-emotional functioning, and may mask these difficulties.

The rationale for exploring amygdala functioning

Impaired social and emotional functioning is common to those with epilepsy, especially TLE, and factors for a more severe presentation include chronic epilepsy and childhood-onset, the latter being associated with unrecoverable amygdala damage. Section 9.1.1 will discuss the most appropriate task for assessing amygdala functioning.

7.4.2 Hippocampus

Gupta and colleagues argue that while simple decision making can be performed using emotion-based systems rather than declarative memory, they suggest that there is a significant role of the declarative memory system in the complex decision making required by the IGT (Gupta et al., 2009). Gupta and colleagues state this is because the declarative memory system is implicated in relational memory and relational representations of successive events (ibid, p.1687). They argue that individuals with declarative memory impairments cannot integrate the information needed to track the novel and arbitrary relationships in the IGT, and form a larger integrated understanding of the consequences of each deck over time. Research suggests that the medial temporal lobe structures play an associative role in memory formation. In TLE, semantic relational processing is impaired, not due to the result of inefficient retrieval, but attributed to the role of temporo-limbic structures, as TLE disrupts semantic networks (Helmstaedter, Gleißner, Di Perna, & Elger, 1997; Troster et al., 1995). Unsurprisingly, research has found that category-specific recognition and naming deficits are common in TLE both pre- and post-operatively (Drane et al., 2008). In addition, neuroimaging studies suggest that the

frontal lobes are associated with the organisation of material during encoding, and the fronto-temporal networks play a role in co-ordinating, interpreting and mediating these associations (Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010).

Section 8.3 will discuss the most appropriate task for assessing declarative memory functioning, specifically semantic relational impairments.

Somatosensory cortices

According to Bechara and Damasio, decision making is mediated by large scale structures which include the somatosensory cortices (Bechara & Damasio, 2000). This has been supported by a study employing fMRI neuroimaging (Lawrence, Jollant, Daly, Zelaya, & Phillips, 2009). They describe how emotion is expressed as the representation of body states as a result of the transient changes of activity in the somatosensory structures, hence the term: somatic state. During decision making, pertinent information is activated in a body loop made up of the previously learned factual-emotional set and its ventromedial prefrontal linkages. When changes occur, this activation is relayed via an 'as if body loop' mechanism to the somatosensory cortices eliciting an appropriate activity pattern in the cortices from the somatosensory structures. This has implications for individuals with epilepsy and specifically seizure auras which disrupt somatosensory functioning in these cortices (Santana et al., 2010). Somatosensory auras are found in focal epilepsy, multifocal epilepsy, FLE and mesial frontal epilepsy (Janszky, Fogarasi, Jokeit, & Ebner, 2001; Tuxhorn, 2005). Empirical evidence of severe impairments of somatosensory processing has been found in adults with TLE; see section 4.5 for a detailed discussion (eg. Grant et al., 2005). This suggests that there is a relationship between epilepsy and somatosensory impairment, which may have implications for the 'as if body loop' mechanism during decision making processing. Despite such evidence, since focal seizure auras are under-reported, the full extent of disrupted somatosensory activity caused by epilepsy has still to be established. Failure to learn by adapting behaviour according to changes in stimulus-reward contingencies indicates a dysfunction in reversal learning. Functional differences in reversal learning may be a marker of vmPFC integrity, as not only do patients with vmPFC damage exhibit reversal learning deficits, but this correlates with scores assessing disinhibited and socially inappropriate behaviour (Rolls, Hornak, Wade, & McGrath, 1994). Having discussed why SMH is the best theoretical approach for investigating social cognition in adults with epilepsy, the aim of each specific experiment will now be discussed.

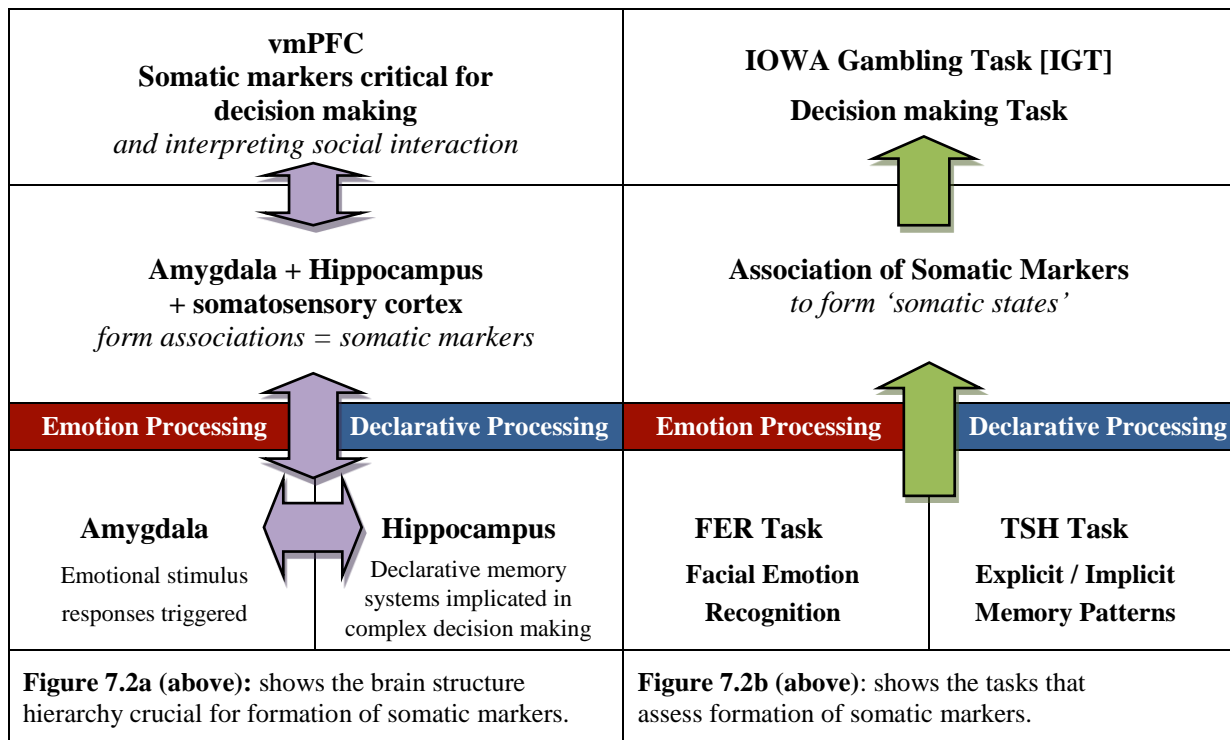
7.5 Main Research Question

A number of studies report that social difficulties may be under-recognised in epilepsy, and many social difficulties have previously been attributed to the psychosocial consequences of having epilepsy. However, epilepsy is a neurological condition, and social cognitive abilities have been largely unexplored when compared to the profusion of research in psychosocial adjustment of adults with epilepsy. The question of whether social difficulties are a result of an underlying deficit of neural substrates which provide the representation of bodily states that underpin decision making abilities and guide social behaviour in adults with epilepsy, is largely unanswered. In order to more clearly address this question, the main research question tests the somatic marker hypothesis by investigating the relationship between decision making abilities as a measure of somatic marker functioning in adults with epilepsy. This examines whether impaired somatic markers underpin differences of social functioning on measures of autistic characteristics. This model provides a framework to investigate the relationship of amygdala and hippocampal functioning which are crucial to somatic marker formation, to evaluate the explanatory power of the SMH model. Critically, if somatic marker formation were impaired, this would suggest that there may be deficits in the expression of emotions in the representation of body states underpinned by the neural systems which play an important role in decision making and may crucially also result in social impairments in adults with epilepsy.

7.6 Aim of Experiments

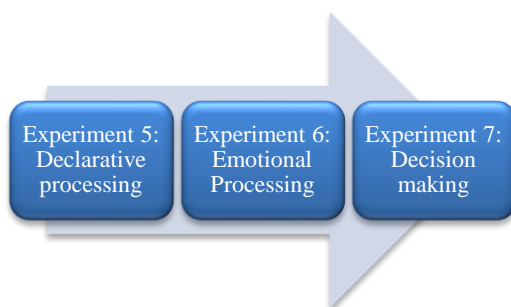
This chapter has evaluated the theoretical framework and this section proposes the most appropriate tasks which may be employed to investigate the brain structures related to the formation of somatic markers, to explore the explanatory power of the SMH, see Table 7.2 for hierarchical structure.

Figure 7.2 Hierarchical structure diagram: Formation of somatic markers, brain structures, and tasks



The evidence discussed in section 7.3.2 lays out the neuroanatomical framework implicated in somatic marker formation, and the mechanisms which underpin their generation (see Figure 7.2a). For clarity, the Somatic Marker Hypothesis as a single model has been divided and presented as three experiments (see Figure 7.2b and 7.3).

Figure 7.3: The single model separated into three experiments to assess framework for somatic marker formation



The background to each experiment is discussed in detail in sections 8.3, 9.1.1 and 9.2.1.

7.7 Rationale for methods used

This hypothesis proposes that these emotion-based biasing signals regulate decision making in complex situations where a detailed cost-benefit analysis is not possible, providing an explanation of

how emotion influences decision making (Damasio, 1994; Damasio et al., 1991). This research seeks empirical quantitative measures from performance on well-validated tasks to explore a theory which has been empirically well researched. However, some participants with adulthood-onset of epilepsy may have acquired adequate social functioning abilities during a typical childhood developmental period. An empirical task which would be difficult for these participants to knowingly guess the outcome is considered to be most appropriate to this experiment. This research project investigates whether the somatic marker hypothesis can provide an explanation for social cognitive functioning in adults with epilepsy. There is a need to establish performance of decision making abilities in a heterogeneous sample of adults with epilepsy, as well as the contribution of amygdala and declarative memory functioning. This research aims to provide a theoretical model for impairments of social cognitive functioning which may explain autistic characteristics in adults with epilepsy, as well as evaluating the explanatory power of this model in terms of underlying functioning which contribute to the somatic marker hypothesis. The IGT explores the relationships of SCR's and decision making; however SCR's will not be assessed in Experiment 7. According to Dunn and colleagues, reliable anticipatory SCR differences have been only been reported in a sub-group of healthy control participants (Dunn, Dalgleish, & Lawrence, 2006). Therefore exploring SCR's would not be advantageous to Experiment 7. Instead, decision making ability will be assessed on task performance and the FER task will be employed as a measure of amygdala functioning. Likewise, EEG will not be employed as detection of spontaneous electrical activity, as measured brain responses are not a focus of this research. The main research experiments do not seek to assess participants with epilepsy during seizure aura activity due to overriding ethical and practical issues.

Experiment 7 aims to precisely investigate decision making ability in adults with epilepsy, and conduct additional exploration for specific functioning processes that contribute to decision making ability. The primary theoretical model employed to address this aim is the Somatic Marker Hypothesis. The overall research aim is to investigate social behaviour in adults with epilepsy, and the rationale for exploring somatic markers is that compromised somatic marker formation may explain social difficulties. Presently, it is unclear what mechanisms underlie this specific deficit, however chronic epilepsy consistently presents as a factor for severity of impairment.

7.8 Anti-epileptic Drugs

AEDs are a factor for improved socio-emotional functioning which may influence performance on the FER and IGT studies, and while TLE is negatively associated with verbal memory deficits, at least one AED is known to cause impairment in complex decision making (Cavanna, 2010).

Summary

Experiments 5-7 explore the SMH in adults with epilepsy. The evidence suggests that SMH is the most appropriate viable theoretical model to investigate social cognitive impairments in adults with epilepsy. The reasoning here is that adults with epilepsy may have previously learned social skills and developed ToM, so a social cognitive deficit does not imply a failure of social learning prior to onset of epilepsy or a developmental social cognitive dysfunction. In addition, adults with epilepsy may or may not have recoverable amygdala damage, and they are most likely to have moderate to severe memory impairments. The relationship of the amygdala and memory impairments in relation to known specific patterns of impairments in ASD will be additionally explored.

Chapter 8

Task Support Hypothesis

8.1 Participants

Experiments 5-7 recruited adults with epilepsy and adults without epilepsy, Group A: a control group of adults without epilepsy; Group B: adults with epilepsy.

8.1.1 Method of Recruitment

Participants were recruited predominantly through response to adverts that asked for adults with and without epilepsy. This used an opportunity sampling method, and included:

Adverts on epilepsy charity websites;

Adverts through University psychology departments;

Adverts in University disability centres;

Recruitment by existing epilepsy participants (snowball sampling);

Recruitment of existing experiment participants;

Advert at 'Open University residential school office' on campus;

Group gender ratios matched, however group mean age was controlled for in the analysis. Limitations of the sample selection are discussed in section 10.7.

Exclusion Criteria

The exclusion criterion from section 5.1.3.1 was employed. No other diagnosis of any co-morbid psychiatric disorder was sought. Additionally, participants without near-to-normal vision were excluded. English-speaking ability was not listed as a requirement as groups were matched for verbal ability (8.1.1). No participant had vagus nerve stimulation designed to prevent seizures, as research has demonstrated that the vagus nerve is a conduit for afferent somatic signals that can influence decision making (Martin, Denburg, Tranel, Granner, & Bechara, 2004).

Recruitment Limitation

This research aimed to recruit a representative group of epilepsy participants; however the research was conducted at the University of Bath requiring the participant to travel to the research laboratory. Therefore, due to travel and length of experiment time, selection may bias towards more high-functioning adults. However, the sampling method was considered the most appropriate available. The control sample consisted of 87.5 % of students; the epilepsy group consisted of 41.7% students, which may account for group age differences.

Intelligence Quotient

Participants were administered two subtests of the WASI which is an abbreviated version of the Wechsler Adult Intelligence Scale-Revised [WAIS-RTM], and provided an index of intelligence (IQ) (table 8.1). Standard instructions for chronological age criteria were employed (Wechsler, 1999). The two-subtests: vocabulary and matrix reasoning, yielded verbal and performance IQ scores (FSIQ-2) reflecting verbal and nonverbal general intelligence and intellectual ability. Each scale has a mean IQ score of 100 and a standard deviation of 15, and the t-score of each subtest has a mean of 50 and a standard deviation of 10 (Wechsler, 1999). This provided a measure of a general cognitive ability, to ensure that any deficits measured were not the consequence of a general cognitive dysfunction.

8.1.2 Clinical and Demographic Characteristics

Epilepsy Group, exclusions

Participant #66 was excluded on the VIQ due to non-response to any word item within the time per item criteria (Wechsler, 1999, p.56). Participant #21 male with epilepsy completed all studies except Experiment 5b, due to time limitations. Participant #37 partially completed, however due to a seizure during testing all data from this participant was excluded. The participant had reported having more seizures than usual before the testing, and a follow-up call after testing suggested that this was attributed to a switch to generic AEDs. See Tables 8.1 - 8.4 for characteristics.

Table 8.1: Demographic characteristics of epilepsy and control groups

Characteristic	Controls (n=16)			Epilepsy (n=12)			Significance
	Mean	SD	Range	Mean	SD	Range	
Gender [Male/Female]	M=4, F=12			M=3, F=9			
Mean Age	28.0	5.92	20-45	36.0	8.47	23-50	$p=0.015$, sig.
Verbal IQ [VIQ]	64.17	8.30	43-73	59.44	7.65	46-71	$p=0.13$, n.s.
Performance IQ [PIQ]	60.75	4.71	50-66	59.0	5.77	49-66	$p=0.39$, n.s.
WAIS-R FSIQ-2	117.19	8.83	102-130	120.75	11.02	93-136	$p=0.35$, n.s.
Education [years]	7.10	2.84	2-12	7.10	1.86	4-9	$p=0.87$, n.s.*.
Age at onset of epilepsy				18.6	9.90	0.3-33	
Duration of epilepsy				18.0	12.10	4.0-43	

* Mann-Whitney U test

Chronological Age

An independent t-test was conducted to explore age differences between group (with/without epilepsy); Kolmogorov-Smirnov test was non-significant revealing normal distribution ($p>.05$), and Levene's test confirmed homogeneity of variance ($p>.05$). There was a significant difference between group ($t=-3.067$, $df=26$, $p=0.005$).

Table 8.2: Classification by primary and secondary type, and known pathology

#	Primary Type	Known Pathology
21	Temporal Lobe Epilepsy, Both Hemispheres - secondary Tonic Clonic seizures	Dispersed brain damage, lack of oxygen
70	Right frontal lobe epilepsy, left temporal discharge - secondary generalised seizures **	Right frontal cortical dysplasia
88	Complex Partial Epilepsy	Scar tissue from brain stem tumour removal
101	Juvenile Myoclonic Epilepsy, - secondary Tonic Clonic seizures	
109	Familial Epilepsy	Genetic link
125	Temporal Lobe Epilepsy, Right - secondary Tonic Clonic seizures	
160	Frontal Lobe Epilepsy - secondary Right Mesial Temporal (treated with VNS)	
164	Idiopathic Generalized Epilepsy	
190	Tonic Clonic Epilepsy - secondary Absence seizures	
191	Temporal Lobe Epilepsy, Right	Scarring on right temporal lobe
201	Tonic Clonic Epilepsy	Hereditary
204	Frontal Lobe Epilepsy, Left	Surgery to remove arteriovenous malformation of the left temporal lobe; Todd's paresis: full recovery

* All classification of epilepsy type was self-reported by participants

** ILAE (2009) revision of terminology has replaced the term *secondarily* [secondary] generalised seizure to the specific seizure components (Berg et al., 2010, p.680)

Table 8.3: Classification of epilepsy type

Classification of epilepsy	N	%
<i>Primary Type:</i>		
Temporal Lobe Epilepsy	4	33.3
Frontal Lobe Epilepsy	2	16.7
Tonic Clonic Epilepsy	2	16.7
Other Focal Epilepsy	1	8.3
Juvenile Myoclonic Epilepsy	1	8.3
Idiopathic Generalised Epilepsy	1	8.3
Familial Epilepsy	1	8.3
Total	12	100.0

Table 8.4: Other Clinical Characteristics

Clinical Characteristics	N	%
<i>Hemisphere:</i>		
Left	1	8.3
Right	4	33.3
Both	1	8.3
Unknown	6	50.0
<i>Surgery:</i>		
Brainstem tumour removal	1	8.3
LTLE Venus malformation removal	1	8.3
No Previous Surgery	10	83.3
<i>Seizure Frequency:</i>		
Daily	4	33.3
Weekly	2	16.7
Monthly	2	16.7
Yearly	3	25.0
Unknown	1	8.3
<i>Onset of Epilepsy:</i>		
Childhood-onset <18yrs	3	25.0
Adulthood-onset >18yrs	8	66.7
Unknown	1	8.3
<i>Temporal Lobe Epilepsy:</i>		
TLE	4	33.3
No-TLE	8	66.7
<i>AED Control:*</i>		
Poorly controlled	3	25.0
Partially controlled	2	16.7
Reasonably well controlled	2	16.7
Well controlled	1	8.3
Unknown	4	33.3

**Participants were not required to rate whether they were receiving monotherapy or polytherapy, as this was not the aim of this research.*

Risk Assessment

The studies were conducted in the UoB Psychology Laboratory, which was risk assessed for participants with epilepsy employing the Epilepsy Safety Check Assessment with additional information incorporated from the Epilepsy Risk Assessment (Connections, 2008; Epilepsy, 2010). Missing from the epilepsy risk assessments were psychological factors known to increase risk of seizures. These include environmental stress triggers such as environmental sensory stimuli and stressors, therefore the researcher decided to control for psychological factors which may increase risk during the assessment procedure by conducting an additional assessment for these psychological stressors. A log book was kept to record unplanned participant illness and factors affecting comfort during the research.

Assistance

The researcher was present during testing at all times, and is a Trained Adviser for the National Society of Epilepsy. General first aid response for epilepsy participants was provided by a qualified assistant, who is AED administration certified at NVQ2 level. Emergency first aid was provided by UoB Security Services for any incident requiring an immediate response. A second assistant was available on-call, on campus.

Design

The design of each experiment is reported in sections 8.5.3, 9.1.2.3 and 9.2.2.3. No analysis was conducted assessing participants with epilepsy during epileptic activity, as it would be impractical to wait and unethical to necessitate these participants to experience epileptic activity during the research.

Procedure

Participants were invited to take part in research of memory, perception and social cognition at the UoB lasting approximately 1.5 hours, and given a brief consent form. The invitation to take part offered all participants a £5 gift voucher or chocolates, and up to £50 travel reimbursement fees. Participants were advised to bring glasses or contact lenses if they would normally wear them. New participants were invited to complete the Autism Quotient. All participants with epilepsy were given a short break after arrival before the start of their testing. All participants read through the consent form which communicated the research aims and what would be involved during the research process. In addition, the researcher read out the consent form to all participants with epilepsy, to ensure that it had been understood. The researcher informed the participant about the experiments and that their participation was voluntary. The participants were informed that they could withdraw at any time

without giving any reason. Participants were invited to read, ask questions, and sign their informed consent, and were provided with a copy. Each participant was informed that their travel would be reimbursed regardless of their decision to take part. All participants were tested individually. Participants with epilepsy were invited to bring along a friend/carer. Friends and carers were invited to either sit in the adjoining kitchen or in the laboratory during testing. The researcher started the research when the participant was ready. Experiments 5, 6 and 7 and each WASI subtest were undertaken during the testing in a randomised order to avoid Order Effects and Fatigue Effects. Experiments 5a and 5b were counterbalanced for order effects [see 8.5.3]. For each experimental procedure, see 8.5.4, 9.1.2.4 and 9.2.3.4. Participants were given 5 minutes rest between each experiment and asked before each succeeding experiment if they were ready to continue.

Ethical considerations

This research was approved by the UoB Department Of Psychology Ethics Committee, [refs: 10-745; 10-746; 10-747], which upholds the ethical standards of the British Psychological Society Code of Ethics for human for research. Ethical considerations are outlined on the consent form (Appendix F). Consent forms and all research data were stored at UoB. Participants were assured that participation was anonymous and they would not be personally identifiable as all data was stored under a reference code, and protected from unauthorised use and from theft. Research aims were clearly communicated and there was no deception. Participants could withdraw from participating at any time and without giving any reason. No participant's safety was endangered during this research, and the research was deemed not to include any threats to self-esteem. All participants were treated with respect, and every effort was made to ensure each participant felt comfortable during the testing and before starting each task. At the end of the testing, the participant was thanked, offered an opportunity to ask questions and asked to provide feedback. No psychological or other advice was offered to epilepsy participants, or their carers or spouses. However, participant #164 was provided with two epilepsy helpline phone numbers in response to complaints of spousal bullying. There was no overall time limit, and adequate rests were provided between tasks. Participants were allowed to decline any information requested by the researcher, and this did not prevent the participants taking part in the research. The results of group differences were sent to all participants by email or post and disseminated to three epilepsy charities (Appendix G). Note that these results include a visuo-perceptual task which was undertaken but not reported in this thesis.

8.1.3 Analysis

All analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 14.2 and version 16.0 and Predictive Analytics SoftWare (PASW) version 18.0 for Windows. No analysis was undertaken during Experiments 5-7 to explore factors of childhood/adulthood-onset, epilepsy type,

AED control, TLE or no TLE, frequency of epilepsy, hemisphere, or gender of participants, due to small group numbers. This chapter will now report on Experiment 5, the overall background to this experiment has been outlined in Chapter 7.

Task Support Hypothesis, Experiment 5

Patients with TLE may reveal some memory patterns similar to those found in the TSH, and in those with ASD. However, no research has been conducted employing ‘The Task Support Hypothesis’ in adults with epilepsy, and this experiment aims to fill this gap.

8.2 Experiment 5a: Semantic Relational Processing in Free Recall

Experiment 5a is a test of use of category information at encoding.

Experiment 5b: Read and Generate Processing of Implicit and Explicit Words with Cued Recall

Experiment 5b is a test of two encoding conditions, and two recall conditions of implicit and explicit memory tests.

8.3 Background

The evidence suggests that relational memory is important for binding together the elements necessary for sustained complex decision making abilities and crucial to somatic marker formation. Importantly, the ventromedial sector holds linkages between declarative facts and the emotions previously paired with this according to the individual’s contingent experience. This section will now evaluate the most appropriate task for assessing relational memory and declarative processing.

Task Support Hypothesis

According to Bowler and colleagues, those with ASD have difficulties in processing complex information, demonstrated by a pattern of impairment of semantic relational memory, while memory is spared for single items that are non-relational (Gaigg, Gardiner, & Bowler, 2008). This has been demonstrated by tasks in which the researchers manipulated conditions during the encoding and retrieval stages with adults with ASD (Bowler, 1997). They found that participants with ASD fail to use category information, while superior recall in explicit testing and superior completion in implicit testing was intact, and there was a significant improvement where support was available. In addition, there was no difference in baseline and intrusion rates at recall, suggesting that intact cued recall in AS was not a result of automatic processes. The researchers termed their hypothesis ‘The Task Support Hypothesis’ as those with ASD perform better with support at task level to aid recall.

Consistent with this is a study by Phelan and colleagues which showed that those with ASD have a specific deficit in organising information (Phelan, Filliter, & Johnson, 2011).

Later research by Bowler and colleagues reveal specific findings: i) participants with ASD do not demonstrate reduced forgetting rates for arousing stimuli (Bowler, 2008); ii) relationships presented as random and categorised words at encoding help ASD and controls equally, however, iii) relationships at encoding lead to reduced recall in smaller item categories, revealing specific difficulties in relational but not item-specific encoding in ASD (Bowler, Gaigg, & Gardiner, 2008; Bowler, 2008; Gaigg et al., 2008); iv) participants with ASD were less likely to cluster items together at recall, v) enhanced recall occurs when category labels are provided (Bowler, Gaigg, & Gardiner, 2010; Gaigg et al., 2008). Bowler and colleagues explored performance in those with ASD to frontal lobe patients and their results suggest that the medial temporal lobe [MTL] may not adequately provide information to the frontal lobes for strategic processing (Bowler et al., 2010). In support of Bowlers hypothesis, a recent fMRI investigation has demonstrated that adults with ASD have regional variations in neural activity during detection of semantic incongruities compared to adults without ASD (Catarino et al., 2011). These findings are consistent with the hypothesis that people with ASD have impaired integration of multiple neural networks, supporting earlier research which showed that compared to those without ASD, those with ASD demonstrate atypical electrophysiological responses to congruent final words in written sentences (Ring, Sharma, Wheelwright, & Barrett, 2007).

The use of a memory strategy in epilepsy has previously been employed in a task which demonstrated that the use of self-generation at encoding facilitates improved cued recall and recognition memory in adults with seizure disorders, predominantly TLE and FLE, but found no improvement for free recall (Schefft et al., 2008). Schefft suggests that a memory encoding strategy that actively involves patient participation enhances some types of memory performance, but highlighted factors negatively influencing memory in epilepsy, including early onset, duration, seizure frequency, and AEDs. Conversely, successful surgery can sometimes reverse memory loss (Alessio et al., 2006). Deficits of semantic relational processing are common in TLE, and have been attributed to the role of temporo-limbic structures as TLE disrupts semantic networks (Helmstaedter et al., 1997; Troster et al., 1995). It has recently been demonstrated that differences in networks may be responsible for deficits in semantic access on word retrieval tasks in TLE. Researchers employing fMRI found that those with both left and right MTLE use more posterior temporal regions in comparison to controls who use more anterior temporal and prefrontal regions (Protzner & McAndrews, 2011). This research goes beyond the current emphasis on the role of lateralisation in semantic processing.

Potential Limitations

Bowler found that explicit memory was intact in ASD, however, the difference of impairment on tests of explicit memory in TLE between left and right can be significant, and performance in some adults with right TLE can be within the normal range (Andrewes, 2002). While the hippocampus can recover from acquired damage, impairments on tests of explicit memory in TLE tend to be demonstrated by those with known hippocampal damage, as there is a strong association between explicit memory and mesial temporal lobe integrity. However, research is arguably dominated by assessing recovery from surgical intervention and the investigation of AEDs, and the present literature on TLE may not be fully representative of the broader pattern of memory functioning in adults with epilepsy.

The rationale for exploring semantic memory functioning

Experiment 5 looks for evidence of TSH in adults with epilepsy. This not only allows investigation into the exploratory power of the SMH, but also seeks for specific and selective memory impairments which are demonstrated by those with ASDs, in a heterogeneous epilepsy sample.

8.4 Aim

This experiment investigates the Task Support Hypothesis in adults with and without epilepsy. It will replicate Bowler's design and stimuli. The first aim sought to determine whether similar memory patterns exist in adults with epilepsy, by replicating the original study tasks by Bowler and colleagues, to assess the TSH. The second aim is to evaluate the relationship of these memory processing abilities to the formation of somatic markers. It is hypothesised that adults with epilepsy will demonstrate memory patterns similar to those with ASD, and that the TSH may offer viable model for memory support. This research is important because it evaluates declarative memory, specifically relational memory, which is implicated in the integration of novel and arbitrary relationships in the IGT.

Hypotheses

Experiment 5a:

H1: There will be a difference in recall of related words between adults with and without epilepsy; adults with epilepsy will demonstrate poorer recall of related, but not unrelated words.

Experiment 5b:

H1: There will be no difference between adults with and without epilepsy between explicit and implicit tests.

H2: There will be superior recall for both groups of explicit generated words and implicit read words

8.5 Method

8.5.1 Participants

Experiment 5a comprised: Control Group $n=16$ [Female $n=12$, Male $n=4$], Epilepsy $n=12$ [Female $n=9$; Male $n=3$]. Experiment 5b comprised: Control Group $n=16$ [Female $n=12$, Male $n=4$], Epilepsy $n=10$ [Female $n=8$; Male $n=2$] (section 8.1).

Exclusions

Experiment 5b had 2 exclusions: participant #190, female with epilepsy was excluded, as data revealed 22 intrusion words, indicating the participant had not followed the instructions correctly; participant #21 did not take part (section 8.1.1).

8.5.2 Materials

Experiment 5 used the same stimuli and procedures used by Bowler and colleagues, Experiment 5a replicated Experiment 1, Experiment 5b replicated Experiment 2 (Bowler, 1997).

Experiment 5a: Semantic Relational Processing in Free recall

Experiment 5a is a semantic relational task requiring free recall of category related and unrelated word lists presented verbally. The task comprised of two word lists of twelve concrete nouns matched for frequency of use, which were employed by Bowler and colleagues from a previous experiment by Tager-Flusberg (1991) (see Appendix I). Minor changes are outlined below. List 1: nouns from different categories - unrelated word list, [UWL]. List 2: nouns from a single category of animals – related word list, [RWL]. *Word changes – Experiment 5a:* One word ‘Elephant’ was replaced with “Thumb” in UWL as it clearly related to the RWL category, as the original non-related word list contained words from mixed categories (Tager-Flusberg, 1991, p.420). Two words in the UWL list related to each other (Cabin-Airplane), therefore “Cabin” was replaced with “House”; here, the relationship of the word “cabin” to an aircraft may be due lexical changes in usage and meaning since the original list design in 1991.

Experiment 5b: Read and Generate Processing of Implicit and Explicit Words with Cued Recall

Experiment 5b consisted of 80 different unrelated 6-letter concrete nouns: from the previous study and additional words were added from the Oxford Mini Dictionary (Oxford Mini Dictionary, Thesaurus & Wordpower Guide, 2002). All cards were generated by printing the words from a

computer in black ink on individual white landscape format index cards, 210gsm (148mm x 95mm). See Appendix K for the full word list.

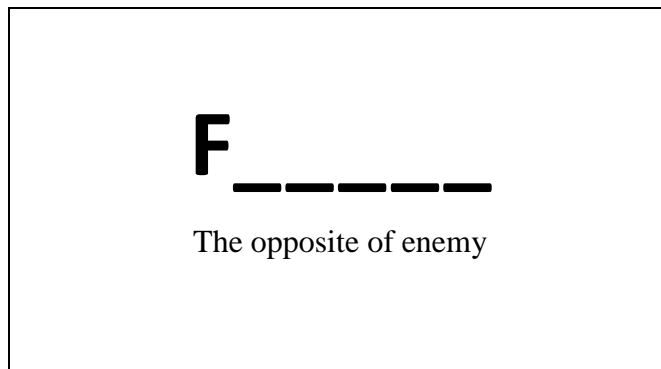
Read:

In the 'read' condition, each word was printed in capital letters, sans serif font, black ink, 60pt centred:



Generate:

In the generate condition, word stems were presented in capital letters, clues were printed below: serif font, 16pt, upper/lower case, centred in a single line:



Scoring

Experiment 5a: was scored by the number of words recalled, ranging from 0-12. Experiment 5b: was scored by the number of words correctly recalled, ranging from 0-20 for each condition of recall (total range=0-40). Scoring rules were based on Bowler's study: phonetical spelling inaccuracies were accepted, $n=3$.

Filler task

A standard Digit Symbol Coding task was employed as a filler task, Appendix L.

Response Sheets

Two response sheets for hand-written responses were employed in the implicit or explicit test, and order of presentation was counterbalanced, Appendix K. Each response sheet consisted of 40 3-letter words stems of 20 ‘Studied’ words and ‘20’ Novel words. The Novel words had not previous been presented to the participant for experiment, and provided a baseline measure of priming and intrusion rates during recall. The 20 studied words were taken half from the generate word list and half from the read list.

8.5.3 Design

Experiment 5a

Experiment 5a was conducted as a between-groups design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV were scores of correctly recalled stimuli from the related and unrelated word list.

Experiment 5b

Experiment 5b was conducted as a between-groups design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV were scores of correctly recalled words in implicit and explicit recall conditions from two sets of encoding conditions: generate or read.

8.5.4 Procedure

The procedure replicated Bowler’s studies (Bowler, 1997). Each participant sat at a table facing the researcher, and stimuli were kept hidden until presented.

Experiment 5a

The researcher read out standard instructions, and participants were invited to ask questions before starting (Appendix H). Participants were asked to listen carefully and to recall as many words as they could immediately after the researcher had finished. Words were presented verbally at an approximate rate of one word per second; the timing of verbal presentation was practiced beforehand by the researcher using a stopwatch. Responses were recorded by the researcher. There was no time limit for recall; the task lasted approximately 5 minutes. The researcher recorded the occurrence of clustering during recall, as individuals with ASD show reduced clustering (Bowler et al., 2009).

Counterbalancing

Each list word order was presented randomly, and lists were counterbalanced to eliminate order effects.

Observations

Six participants with epilepsy and two control participants reported using a memory strategy; however most participants recalled their words in presentation order ($n=25$), suggesting they had employed a memory strategy. The control participants did not provide details of their strategy, however the epilepsy participants immediately described their chosen strategy in detail and reported using the word order to help them recall the words. One participant described in incremental detail a mental journey around the rooms of their house and relating each noun to this journey.

Experiment 5b

This experiment took part in three stages: encoding, filler task, recall.

Encoding

Participants were informed that after presentation, there would be two filler tasks before they were given a memory test. The researcher read out standard instructions (Appendix J). Index cards were placed face-down in front of the participant. The researcher selected the top card and individually presented the stimulus to the participant at a rate of one card every five seconds, the timing of presentation was measured using a digital stopwatch. The participants spoke the target word aloud, and prompts were provided replicating Bowlers procedure. After the presentation, each card was placed face-down so that the word was hidden from view. This procedural change to the original study was incorporated after a pilot test revealed that cards placed face-up after presentation distracted the participant's attention. No participant failed to generate any word.

Filler task

In Bowler's original study, half the subjects were given the Mill Hill Vocabulary Test and half the Digit Symbol test, so each participant only completed one filler task. However, participants were already undertaking a Vocabulary Test to provide a measure of verbal ability for the FSIQ-2. Therefore, these 2 filler tasks employed were replaced in Experiment 5b by one filler task 'Digit Symbol Coding' task given to all participants. This was considered adequate as a single filler task, since the purpose of the filler task was to prevent the implicit test becoming contaminated from consciously controlled uses of memory should the participants recognise the items they produce from the earlier phase in the experiment, and ensures that the participants would be less likely to recognise the implicit test as a memory test. The researcher presented the filler task to the participant and instructed the participant to complete the task in a left-to-right sequence. After 5 minutes participants were asked to stop.

Recall

Recall was completed in two conditions: the implicit memory test and the explicit memory test. The researcher wrote 'filler task' on the first response sheet presented, and 'memory test' on the second response sheet presented while the participant watched, so that participants were not made aware the implicit task was a memory test. For the implicit test, the participant was instructed to quickly complete as many of the words as they could with the first word that came to mind excluding proper nouns. For the explicit test, the participant was informed that they would take a memory test, and instructed to use the initial stems to remind them of the words that they had studied before. Participants were asked not to guess, and they were told that only half of the word stems have been previously shown to them (studied), therefore half of the words were new (novel). There was no time limitation, and the task lasted approximately 25-30 minutes.

Counterbalancing

The order of presentation of stimuli was counterbalanced to present both 'studied' and 'novel' stimuli. This was achieved by counterbalancing 2 card sets: Set A and Set B at encoding, so that the Set presented was 'studied' and the non-presented set was 'novel'. In addition, the two response sheets were counterbalanced at the recall stage.

Card Sets

Only Set A or Set B was shown to participants. Set A or Set B stimuli cards consisted of 40 words (20 generate/20 read). Therefore, each participant was presented with 40 words at encoding. However, all participants were tested for all 80 words, 40 words from Set A and 40 words from Set B, and therefore half of the words were 'novel' and half were 'studied'.

Observations

Five control participants asked if the implicit 'filler' task was a memory test, and the researcher repeated that it was a filler task. Three epilepsy participants reported finding Experiment 5b difficult.

8.5.5 Ethical Considerations

Ethical considerations have been outlined previously and participants were informed of the task aims (section 8.1.2).

Analyses

All analyses for Experiments 5-7 were carried out using Statistical Package for the Social Sciences (SPSS) version 14.2 and version 16.0. Significance level was set at a conventional level of 5%

throughout the research. As this research is primarily exploratory, trends approaching this level of significance will be reported: approaching significance = 0.051-0.99 significance. The reason is that to ignore any trends may exclude areas of importance.

8.6.1 Experiment 5a Results

Analysis was conducted employing an independent t-test and an ANCOVA controlling for age. Kolmogorov-Smirnov test revealed normal distribution ($p>.05$), and Levene's test confirmed homogeneity of variance ($p>.05$) for word recall and word interferences.

Word Recall

Analysis explored differences of recall of *related* words between groups. An independent t-test was approaching significance between groups ($t=1.99$, $df=26$, $p=0.057$, *n.s.*). An ANCOVA with age as a covariate was conducted to account for age differences (see demographics, Table 8.1), which revealed no significant difference between group ($F_{(1,25)}=1.85$, $MSE=3.98$, $p=0.19$, *n.s.*). Analysis explored differences of recall of *unrelated* words between groups. An independent t-test was approaching significance between groups ($t=1.97$, $df=26$, $p=0.060$, *n.s.*), an ANCOVA also revealed this was approaching significance, revealing a trend for adults with epilepsy to recall fewer unrelated words ($F_{(1,25)}=3.35$, $MSE=5.22$, $p=0.079$, *n.s.*), see Table 8.5.

Word Interferences

Analysis explored differences of recall of related and unrelated interferences between groups. An independent t-test and ANCOVA revealed there was no significant difference for *related* word interferences ($t=-.554$, $df=26$, $p=0.58$, *n.s.*; $F_{(1,25)}=1.69$, $MSE=7.43$, $p=0.21$, *n.s.*), or for *unrelated* word interferences ($t=-.474$, $df=26$, $p=0.64$, *n.s.*; $F_{(1,25)}=0.99$, $MSE=6.41$, $p=.33$, *n.s.*), see Table 8.5.

Table 8.5: *Related and Unrelated Words Memory Task*

	Words Recalled			Interferences		
	Related	Unrelated		Related	Unrelated	
	Mean (SD) Range	Mean (SD) Range		Mean (SD) Range	Mean (SD) Range	
Controls $n=16$	7.25 (2.11) 4-11	6.94 (2.27) 3-11		0.31 (0.78) 0-3	0.44 (0.63) 0-2	
Epilepsy $n=11$	5.75 (1.77) 3-9	5.25 (2.22) 2-10		0.50 (1.0) 0-3	0.58 (1.0) 0-3	
<i>Sig. p-value</i>	$p=0.19$, <i>n.s.</i>	$p=0.079$, <i>n.s.</i>		$p=0.21$	$p=0.33$	

Years of Epilepsy

Pearson's correlation coefficient explored the relationship between 'years of epilepsy' and recall, [$n=11$; missing $n=1$]. The analysis was approaching significance for related words, with fewer words being recalled in chronic epilepsy, $r=-0.49$, $p=0.065$ (*one-tailed*) *n.s.*, and non-significant for unrelated words, $r=-0.27$, $p=0.21$ (*one-tailed*).

Order of Presentation

Analysis explored differences of recall in order of presentation of words. Kolmogorov-Smirnov test revealed normal distribution ($p>.05$). Levene's test confirmed homogeneity of variance ($p>.05$). An independent t-test revealed that there was no significant difference between presentation for related words ($t=.49$, $df=26$, $p=0.63$, *n.s.*), or for unrelated words ($t=-.73$, $df=26$, $p=0.47$, *n.s.*).

8.6.2 Experiment 5b: Results

As baseline and intrusion rates are not identical in means, in contrast to Bowler's analysis procedure, all further analyses were conducted on corrected word completion rates, excluding intrusions.

Word Recall

Analysis exploring word recall employed the same statistical procedure as the original study. A one-way repeated measures ANCOVA [General Linear Model 5] with 2 factors as a repeated measure (encoding: generate/read; recall: explicit/implicit) and age as a covariate, was conducted on the data. Mauchly's test for sphericity was significant ($p<.05$), therefore values reported are corrected by a conservative correction factor applied to the degrees of freedom used, Greenhouse-Geisser correction. No difference in overall performance between the two groups ($F_{(1,23)}=0.006$, $MSE=0.059$, $p=0.937$). Significantly more items were completed in the implicit condition [mean=11.81] than explicit condition [mean=9.35] ($F_{(1,23)}=15.85$, $MSE=78.77$, $p=.001$). The group by implicit/explicit performance was not significant ($F_{(1,23)}=0.186$, $MSE=0.65$, $p=0.67$). The group by generate/read performance was not significant ($F_{(1,23)}=0.027$, $MSE=0.032$, $p=0.87$). The interaction between encoding by recall by group was not significant ($F_{(1,23)}=2.45$, $MSE=18.0$, $p=0.131$). The interaction between two within-subject variables (implicit/explicit by generate/read) for both groups was significant ($F_{(1,23)}=17.1$, $MSE=129.4$, $p=0.001$), see Table 8.5.

Explicit Word Recall

Epilepsy is well-known to impact upon explicit memory, researchers have suggested that compromised explicit memory is a factor for impaired performance on the IGT. Therefore analysis was conducted to explore group differences for total explicit recall (generate + read). Kolmogorov-

Smirnov test revealed normal distribution ($p>.05$). Levene's test confirmed homogeneity of variance ($p>.05$). An independent t-test and ANCOVA revealed that there was no significant difference ($t=1.44$, $df=24$, $p=0.16$, $n.s$; $F_{(1,23)}=0.58$, $MSE=14.1$, $p=0.46$, $n.s$). See Table 8.6.

Table 8.6: Encoding and Recall of words

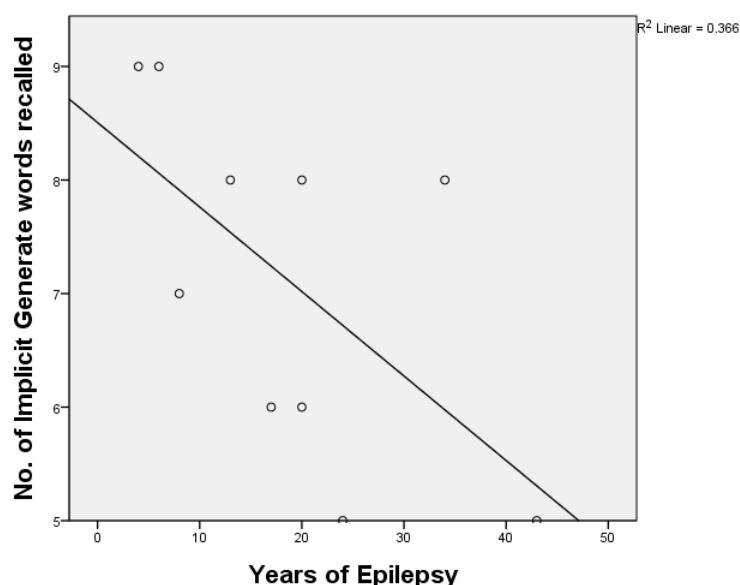
	Explicit Words Recalled			Implicit Words Recalled	
	Generate	Read	Intrusions	Generate	Read
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range
Controls $n=16$	5.69 (1.66) 4-9	4.50 (2.48) 0-9	2.25 (2.79) 0-9	6.25 (1.57) 3-9	5.81 (1.80) 3-9
Epilepsy $n=10$	4.50 (2.12) 2-8	3.50 (2.84) 0-7	1.30 (1.56) 0-5	7.10 (1.52) 5-9	5.50 (1.84) 3-9
<i>Sig. p-value</i>	$p=0.48$, $n.s.$ *	$p=0.56$, $n.s.$ *	$p=0.46$ *	$p=0.072$ *	$p=0.86$ *

* Analysis of Covariance

Years of Epilepsy

Epilepsy is well-known to impact upon memory across time. Therefore Pearson's correlation coefficient analysis was conducted to explore the relationship between 'years of epilepsy' and recall, [$n=10$]. There was a significant difference, revealing a negative relationship between implicit generate words recalled and 'years of epilepsy' in adults with epilepsy, $r=-0.61$, $p=0.032$ (*one-tailed*) sig., see Figure 8.7. Analysis was approaching a trend towards a negative relationship for explicit generate words recalled and 'years of epilepsy', $r=-0.51$, $p=0.068$ (*one-tailed*), there was no significant relationship for 'years of epilepsy' and recall of implicit read words, $r=-0.44$, $p=0.10$ (*one-tailed*) $n.s.$, or recall of explicit read words, $r=-0.178$, $p=0.31$ (*one-tailed*) $n.s.$

Figure 8.7: Number of Implicit Generate words recalled and 'years of epilepsy'



8.7 Discussion

The aim of this experiment was to explore differences of memory patterns in adults with and without epilepsy.

Experiment 5a:

Experiment 5a explored relational memory, and it was hypothesised that adults with epilepsy would demonstrate poorer recall of related but not unrelated words. The results from Experiment 5a showed that there was no significant difference in free recall between adults with and without epilepsy.

Therefore, the null hypothesis cannot be rejected. These results are inconsistent with some research demonstrating that impaired semantic relational processing is common in TLE (Helmstaedter et al., 1997; Troster et al., 1995). These results are also inconsistent with the TSH. ‘Years of epilepsy’ was found to be approaching significance for related words but not unrelated words, suggesting that chronic epilepsy is related to poorer recall of related words.

Previous research has explored factors for impairments in semantic relational processing during a verbal free recall task in patients with TLE, and found that strength of memory functioning can vary according to lateralisation, frequency and type of seizures (Helmstaedter et al., 1997; Hendriks et al., 2004). However, the role of lateralisation has been challenged by recent fMRI neuroimaging study which demonstrated that lateralisation is not a key factor (Protzner & McAndrews, 2011). Experiment 5a did not reveal such impairment, and no analysis explored the impact of hemisphere. Other factors known to influence memory functioning such as AEDs were not also investigated due to the study limitations stated below.

Experiment 5a provided a measure of performance of relational memory, implicated in the integration of novel and arbitrary relationships in the IGT. However, there was no significant difference in performance on this task. There may be several reasons why this experiment has not found any group differences. One explanation for lack of findings in Experiment 5a may be use of memory strategies. There was no ‘Clustering’ by either group noted during recall. This is important because individuals with ASD demonstrate diminished clustering during recall according to the study list categories in the task (Bowler et al., 2009). No instruction was given to participants to prevent them using a memory strategy as this would deviate from Bowlers procedure. Neither were participants explicitly asked if they had used a memory strategy. Despite this, order of recall suggested that both groups used memory strategies, and participants from the epilepsy group reported using a memory strategy for the task and they also described their strategies in detail. A second explanation may be that the task was too easy for the epilepsy group as the category might have been easily noticeable. Gaigg and colleagues demonstrate more severe category free recall impairments in lists with fewer items compared to lists with a greater number of items which suggests the numbers of items in the

experimental design was satisfactory (Gaigg et al., 2008). According to Helmstaedter, high associative properties such as ‘Animals’ employed in Experiment 5a would be sufficient to reveal impaired semantic relational processing in LTLE (Helmstaedter et al., 1997). Research suggests that the relational memory processes in ASD may be functionally intact, as effective processing of relational material has been demonstrated by those with ASD where support is provided (Gaigg et al., 2008). In this experiment, identification of the category may have supported the use of a memory strategy. Easy identification of the category may be related to the epilepsy sample (the epilepsy sample is discussed in chapter 10).

In contrast to recall of related words, recall of unrelated words by the epilepsy group was approaching significance. The task employs high associations, the category was easily noticeable, and it is possible that compensatory strategies used were easier to use for the RWL words than UWL words.

Additionally, while the impact of AEDs upon relational and unrelated verbal recall is not known, AEDs have been recognised to influence memory functioning (see 2.10). Despite a trend for chronic epilepsy to negatively influence recall of related words, epilepsy participants did not demonstrate the specific memory pattern of recall differences found in individuals with ASD.

Experiment 5b:

The aim of experiment 5b was to demonstrate that recall in explicit testing and superior completion in implicit testing was intact, and there was a significant improvement where support was available.

Hypothesis 1 stated that there will be no difference between adults with and without epilepsy between explicit and implicit tests, and the results demonstrated no difference between adults with epilepsy who performed similar to those with without epilepsy. Hypothesis 2 stated that adults with and without epilepsy will demonstrate superior recall for explicit generated words and implicit read words. Significantly more items were completed under the implicit than explicit conditions by both groups. There was no difference for encoding (generate/read) by group, or recall (implicit/explicit) by group, nor any three-way interaction. However a significant interaction between two within-subject variables (implicit/explicit by generate/read) was found. Therefore, the experimental hypothesis H1 and H2 is accepted as both null hypotheses can be rejected. Presentation of novel words provided a baseline measure of priming and intrusion rates during recall, and there was no difference in baseline and intrusion rates at recall. All the results in Experiment 5b are consistent with Bowler’s results. Experiment 5b provided a measure of performance of explicit memory, which is crucial for the formation of somatic markers in complex decision making (Gupta et al., 2009). However, there was no significant difference for explicit recall between group.

Experiment 5b results demonstrate the following:

‘Years of epilepsy’ was found to be negatively related to recall of implicit generate words, and approaching significance for a negative relationship with explicit generate words.

The participants with epilepsy did not show any memory impairment in explicit tests;

Performance in Experiment 5b was similar to Bowers hypothesis, in which performance differs from those with amnesic syndrome who fail in explicit but not implicit tests;

Chronic epilepsy negatively impacted upon recall.

As outlined above, differences may be related to epilepsy lateralization and age at onset, within the epilepsy group, that could not be controlled for. As previous research has shown, AEDs are known to impact on cognitive functioning; however this epilepsy group may be a higher functioning group with well-controlled epilepsy. Adults with chronic epilepsy recalled fewer items and this supports previous research by Hendriks, and these adults may represent a sub-group of individuals with poorer memory function within the sample (Hendriks et al., 2004).

Limitations

The limitations for Experiment 5b may be a non-representative sample of adults with epilepsy.

Analysis could not be conducted on other factors which may have impacted on the outcome of this experiment such as AEDs, epilepsy type, and age at onset, due to small sample size.

Summary

The memory patterns found in the epilepsy group were not found in those with ASD, therefore the TSH does not provide a viable model for supporting this group. The epilepsy group demonstrated a slightly better level of performance, with unimpaired performance in both studies, whereas the AS participants in Bowers study demonstrated impaired performance in Experiment 5a and unimpaired performance in Experiment 5b. This is in contrast to previous evidence which suggests that participants with TLE do demonstrate difficulties with relational stimuli. Explanations for why this group performed better are suggested: i) use of a memory strategy, ii) bias sample, and iii) AED intervention. Further studies should include instructions to participants to avoid using any memory strategies, and could be undertaken on participants who are not taking AEDs.

These results suggest that adults with epilepsy can perform well on some memory tasks, which may suggest that they use compensatory techniques, they may perform variably, and/or that intact memory

performance is missing from research due to a publication bias. Differences in decision making performance have been attributed to specific explicit memory deficits (Gupta et al., 2009). The findings of Experiments 5a and 5b will be discussed in relation to somatic marker formation in Chapters 9 and 10.

Chapter 9

Emotional Processing and Decision making

*“Social cognition is an important but
neglected area of study in the field of epilepsy.”*

*Dr. Jane McCagh (2009)
Liverpool Hope University*

9.1 Experiment 6: Facial Emotion Recognition Task

9.1.1 Background

The evidence suggests that the amygdala is crucial to somatic marker formation, and may be impaired in adults with epilepsy; this section will now discuss the most appropriate task for this clinical population. Measuring constructs such as emotions can be difficult to assess unobtrusively with good levels of validity, as such there are many self-reported measures. The amygdala is critical for recognition of emotions from facial expressions, and can be activated by subliminally presented facial expressions in typical individuals which increase or decrease in response to the emotional valence of the stimuli (Adolphs, 2001; Whalen et al., 1998). Facial emotional recognition [FER] is a measure of perception of social cues, and a major component of social cognitive abilities that may be related to an inability to produce somatic markers (Adolphs, 2001; Mah, Arnold, & Grafman, 2005). Importantly, neuroimaging findings employing fMRI scanning while study participants are viewing and judging emotional faces, has provided supporting evidence that representations of somatic states are associated with emotion perception (Winston, O'Doherty, & Dolan, 2003). The DSM-IV-TR diagnostic criteria for AS states that there may be a marked impairment in the use of behaviours such as facial expression to regulate social interaction and communication (APA, 2000). Indeed, many studies find a deficit in male adults with ASD for identifying negative emotions (eg. Ashwin, Chapman, Colle, & Baron-Cohen, 2006). However, in a review of the recent literature published on FER ability in ASD, findings on FER for children, adolescents and high-functioning adults with ASD are inconsistent and contradictory (Harms et al., 2010). The researchers conclude that when the

behavioural studies are reviewed as a whole, they are only slightly more likely to find a deficit of FER in ASD than not (ibid.). Notably though, the relationship of IED activity to FER performance in ASD has not been well-investigated and should be a consideration. However, as other empirical measures have supported the finding of group differences between those with ASD and matched controls, the researchers suggest that either those with ASD use compensatory techniques to perform well, or that behavioural studies may be limited. Recently however, researchers have found that adults with ASD were able to develop perceptual expertise with complex non-face objects, demonstrated by their achievement of an enhanced inversion effect after training (Damiano, Churches, Ring, & Baron-Cohen, 2011). The researchers suggest this has implications for a face processing deficit in children with ASD, suggesting that they may not have the same motivation to attend to faces as typically developing children. While behavioural studies for FER have been criticised for mixed findings, the behavioural method will be employed in this research project in the absence of other technology to empirically measure FER. Interestingly, a significant relationship has been found between FER accuracy and the level of social adaptation for adults with ASDs but not those without (Garcia-Villamizar, Rojahn, Zaja, & Jodra, 2010). Such evidence suggests that measuring FER would be most appropriate for assessing amygdala functioning. However some studies have demonstrated that females with AS perform worse on FER than matched controls such as Golan and colleagues, although these findings are based on 6 ASD and 5 control participants (Golan, Baron-Cohen, & Hill, 2006). Other studies have even smaller gender groups (Golan et al., 2010).

Facial Emotional Recognition Task

There is substantial evidence associating epilepsy with emotion perception recognition impairments, especially in TLE and FLE, and may be a specific feature to FLE (Farrant et al., 2005; Reynders, Broks, Dickson, Lee, & Turpin, 2005). Reynders and colleagues found evidence of impaired fear emotion recognition, especially in TLE. Consistent with this, research of 16 patients with TLE found impairments of emotional intelligence and impaired FER (Walpole, Isaac, & Reynders, 2008). Walpole and colleagues suggest that further research is needed to determine whether a reduction in emotional intelligence is found in other epilepsies or specific to the neuropathy of TLE. Specifically, chronic MTLE has been associated with emotional recognition deficits including FER (Bonora et al., 2011). Meletti and colleagues demonstrated that chronic drug-resistant TLE is associated with FER impairment (Meletti et al., 2009). Further, their results reveal that impaired recognition of facial expression of emotion, particularly fear, is widespread among epilepsy patients, and not confined to TLE alone, and were associated with impaired social judgment of trustworthiness, duration of epilepsy, and QOL. The researchers suggest that their study provides evidence of fear recognition deficit in epilepsy regardless of aetiology, and that amygdala dysfunction associated social cognitive impairments is a consistent feature of TLE. Smaller amygdala volumes are found in those with intractable TLE compared to normal controls, and significantly smaller amygdala volumes are found

in those with TLE and ictal fear than those with TLE alone (Cendes et al., 1994). Ictal fear is an early stage of epilepsy associated with TLE in which patients are totally averse to social interaction, and withdraw from social contact. However, amygdala enlargement is also commonly found in TLE. A neuroimaging study of mTLE patients demonstrated that those with hippocampal damage and no amygdala damage showed enhancement of fusiform activation to fearful faces when compared with a matched mTLE group with amygdala damage but no hippocampal damage (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). This difference was found even though the two groups of patients did not differ otherwise in their clinical epilepsy. However, amygdala damage did alter normal activation patterns in response to fearful faces but this group were impaired as a consequence of amygdala damage. These results indicate that it is amygdala functioning rather than amygdala damage that alters the cortico-subcortical network of regions normally engaged by emotional face expression. In addition, inconsistent performance on FER tasks from the patients with unilateral amygdala damage was found, showing that even patients with amygdala damage and epilepsy can perform on FER tasks comparable to a control group.

Experiment 6 looks for evidence of FER abilities in adults with epilepsy. This not only allows investigation into the exploratory power of the SMH in relation to the amygdala, but also seeks a specific impairment demonstrated by those with ASDs.

9.1.2 Aim

This experiment investigates ability for FER and FER intensity in adults with and without epilepsy. It will employ a standard FER test, Pictures of Facial Affect-revised (Ekman & Friesen, 1976; Harmer et al., 2003). Differences in FER in adults with epilepsy may reflect social and emotional processing differences, and impact upon the formation of somatic markers. This may provide an explanation for the important significant findings which emerged from Experiments 1 & 3 which infers a difference in social functioning. As discussed in Chapter 7, the relevance of these findings suggests that the vmPFC may be implicated in socio-emotional processing and somatic marker formation. Previously, Experiment 2 tested the ability to discriminate emotions from the eyes. The results from this Experiment revealed that adults with epilepsy did not differ in detecting emotion from the eyes to the control group. However, with a small sample size, caution must be applied to the findings of this earlier experiment, as the findings might not reflect a broader sample of adults with epilepsy. Chapter 7 has explained the central importance of the amygdala to socio-emotional functioning, and one limitation is that Experiment 2 focused on detecting emotion from the eyes alone, and therefore it cannot be concluded whether there would be a deficit of FER from this study. For example, research has found that adults with ASD have demonstrated impaired performance in ToM tasks which infers a

deficit of socio-emotional functioning, but demonstrate intact performance on the Adult Eyes test (Spek et al., 2010). One implication of this is the possibility that adults with epilepsy could exhibit a deficit of FER, while empathising abilities remain intact. This would indicate that there may be a relationship of amygdala dysfunction to the self-reported social difficulties highlighted in the initial experiments, and this knowledge would add substantially to the understanding of the results from the earlier experiments. Generally, there is mixed evidence for a deficit of FER in adults with epilepsy; despite this, some researchers suggest that this deficit may be common for all epilepsy types. Clearly, measuring FER would be most appropriate for assessing amygdala functioning and formation of somatic markers. Experiment 6 provides a more comprehensive assessment employing the FER to measure six basic facial emotional expressions, and additionally explore intensity effects (the effect of intensity of facial expression). This experiment is designed to establish the extent to which amygdala functioning is implicated in somatic marker formation, and given the stronger relationship of FER ability to social cognitive functioning, it is hypothesised that adults with epilepsy will demonstrate a decreased ability to recognise face emotions and facial emotion intensity.

The first aim of Experiment 6 is to explore FER and FER intensity processing in adults with epilepsy, as a measure of emotional processing. The second aim of Experiment 6 is to evaluate the relationship of these emotion processing abilities to the formation of somatic markers.

Hypothesis

H1: There will be a difference in facial emotional recognition between adults with and without epilepsy.

9.1.3 Method

9.1.3.1 Participants

The participant group was outlined in Chapter 7; it comprised $n=28$: Control Group $n=16$ [Female $n=12$, Male $n=4$], Epilepsy $n=12$ [Female $n=9$; Male $n=3$]. There were no outlier data points.

9.1.3.2 Materials

Participants were provided with a paper-based version of the facial emotion recognition task (Appendix M). The task assesses the ability to correctly recognise facial expressions of emotion at different intensities, based on 'Pictures of Facial Affect' series (Ekman & Friesen, 1976) and was developed by Harmer and colleagues (Harmer et al., 2003). The task represents a widely used and well-validated standardised series of full face photographs commonly used to assess recognition of

6 basic facial emotions: Happiness, Fear, Surprise, Anger, Disgust, and Sadness. The task comprised of 6 black/white photographs of male/female actors for each emotion: 36 presentations including neutral, presented at 4cm wide x 6cm deep. The photographs represent a variable percentage of emotion: 0% (neutral) and 100% (full emotion). For this experiment, a neutral expression and 5 levels of emotional intensity: (20%, 40% 60% 80% 100%, plus neutral 0%), represented a wide range of emotional intensity. They were presented in random order for emotion, actor, and emotional intensity.

Scoring

The task was scored by the number of correct identifications of emotion and by accuracy of emotional intensity for each correctly identified emotion: 1 point equals a correctly identified emotion; 0 point equals an incorrectly identified emotion; total score range: 0-36. Emotional intensity was rated by the participant as a percentage ranging from 0%-100% [0% represents neutral], and was scored by percentage of variance from the emotional level of intensity that was presented. Emotional intensity ratings for incorrectly identified emotions were excluded. There was no missing data.

9.1.3.3 Design

The experiment was conducted as a between-groups design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV were scores of correctly identified emotions and scores of emotional intensity of correctly identified emotions.

9.1.3.4 Procedure

The task was presented to the participant while the researcher read out standard instructions, pointing to the example provided (Appendix M). Participants were invited to ask questions, asked to complete the task without time limitation and to record their responses by pen. They were verbally instructed to reference throughout the task to compare with other stimuli for emotional intensity. The task lasted 5-10 minutes. The participants were allowed an opportunity to ask questions and provide feedback at the end. Eight participants with epilepsy stated that they found the task difficult to do, and didn't think that they had performed well.

9.1.3.5 Ethical Considerations

Ethical considerations have been outlined previously and participants were informed of the task aims (section 8.1.2).

9.1.4 Results

The test was analysed for group differences in the number of correct identifications of emotion for each emotion, see Table 9.1 below. After the analysis was conducted, an additional parametric test, an ANCOVA analysis with age as a covariate, was also conducted to account for the significant age difference between the groups, see demographics, Table 8.1. This parametric test was performed on the data in the absence of a non-parametric equivalent analysis in SPSS.

Emotion Identification

Analysis explored difference in correct total emotion identification between groups. Kolmogorov-Smirnov test revealed non-normal distribution for the control group which when reversed and recoded, was not correctable by log or square root transformation ($p=.014$), while Levene's test confirmed homogeneity of variance ($p>.05$). Therefore analysis was conducted with a non-parametric test, the Mann-Whitney U test. The Mann-Whitney U test revealed no significant difference between groups ($U=70.0$, $Z=-1.22$, $p=0.22$, *n.s.*). This analysis did not account for age group, and therefore in the absence of a non-parametric equivalent, an ANCOVA with age as a covariate was also conducted (see above, 9.1.4). An ANCOVA revealed no significant difference between group ($F_{(1,25)}=1.00$, $MSE=5.66$, $p=0.33$, *n.s.*). As the data lacked normal distribution this comparison has low power, see Table 9.1.

Table 9.1: Facial Emotional Identification Scores

	Controls (n=16)			Epilepsy (n=12)			Significance
	Mean	SD	Range	Mean	SD	Range	sig.*
Anger	3.13	(0.98)	2-5	3.42	(0.90)	2-5	$p=0.88$, <i>n.s.</i>
Disgust	2.37	(0.62)	1-3	2.42	(1.08)	0-4	$p=0.85$, <i>n.s.</i>
Fear	3.63	(0.81)	2-5	3.25	(1.36)	0-5	$p=0.56$, <i>n.s.</i>
Happiness	3.31	(1.01)	2-5	3.08	(1.17)	2-5	$p=0.46$, <i>n.s.</i>
Surprise	4.13	(0.96)	2-5	3.33	(1.50)	0-5	$p=0.35$, <i>n.s.</i>
Sadness	2.87	(0.62)	2-4	2.67	(0.78)	2-4	$p=0.52$, <i>n.s.</i>
Total	19.44	(2.40)	15-24	18.17	(3.79)	11-24	$p=0.33$, <i>n.s.</i> *

* Analysis of Covariance, data lacks normal distribution

Emotion Identification for each emotion

Analysis explored differences in identification of each emotional expression between groups, see Table 9.1. For each emotional expression, data values \leq zero were recoded into positive values. Kolmogorov-Smirnov test revealed negatively skewed distribution for the control group which when reversed, was not correctable by log or square root transformation ($p=.003$), while Levene's test confirmed homogeneity of variance ($p>.05$). Therefore analysis was conducted with a non-parametric

test, the Mann-Whitney U test. There was no significant difference between groups for Anger: ($U=79.0$, $Z=-0.83$, $p=0.41$, *n.s.*, $F_{(1,25)}=0.23$, $MSE=0.02$, $p=0.88$, *n.s.*); Disgust: ($U=85.5$, $Z=-0.53$, $p=0.60$, *n.s.*, $F_{(1,25)}=0.39$, $MSE=0.03$, $p=0.85$, *n.s.*); Fear: ($U=82.0$, $Z=-0.69$, $p=0.49$, *n.s.*, $F_{(1,25)}=0.35$, $MSE=0.41$, $p=0.56$, *n.s.*); Happiness: ($U=82.5$, $Z=-0.65$, $p=0.52$, *n.s.*, $F_{(1,25)}=0.57$, $MSE=0.68$, $p=0.46$, *n.s.*); There was a trend for Surprise which was approaching significance, the epilepsy group mean score was lower than the control group ($U=65.5$, $Z=-1.49$, $p=0.07$ (*one-way*), *n.s.*, although this was not significant when age was controlled for, $F_{(1,25)}=0.91$, $MSE=1.34$, $p=0.35$, *n.s.*); there was no significant difference for Sadness: ($U=78.0$, $Z=-0.92$, $p=0.36$, *n.s.*, $F_{(1,25)}=0.42$, $MSE=0.21$, $p=0.52$, *n.s.*).

Emotional Intensity

Analysis explored differences in identification of emotional intensity between groups, and is reported in Table 9.2. Kolmogorov-Smirnov test revealed positively skewed distribution for the control group which when reversed, was not correctable by log or square root transformation, while Levene's test confirmed homogeneity of variance ($p>.05$). Therefore analysis was conducted with a non-parametric test, the Mann-Whitney U test. The Mann-Whitney U test revealed no significant difference between groups ($U=76.0$, $Z=-0.93$, $p=0.35$, *n.s.*). An ANCOVA revealed no significant difference between groups ($F_{(1,25)}=0.49$, $MSE=11.7$, $p=0.49$, *n.s.*). As the data lacked normal distribution, this comparison has low power.

Emotional Intensity for each emotion

Analysis explored differences in identification of each emotional expression between groups. As this research project was exploratory, trends and non-significant values are reported in Table 9.2. For each emotional expression, data values \leq zero were recoded into positive values. Kolmogorov-Smirnov test revealed negatively skewed distribution for the control group which when reversed, was not correctable by log or square root transformation ($p=.001$), while Levene's test confirmed homogeneity of variance ($p>.05$). Therefore analysis was conducted with a non-parametric test, the Mann-Whitney U test. The Mann-Whitney U test revealed no significant difference between groups for Anger: ($U=89.0$, $Z=-0.33$, $p=0.75$, *n.s.*, $F_{(1,25)}=0.12$, $MSE=58.1$, $p=0.92$, *n.s.*); approaching a significant difference for Disgust with a less accurate mean score by the control participants: ($U=71.0$, $Z=-1.16$, $p=0.25$, *n.s.*, $F_{(1,25)}=3.08$, $MSE=8560$, $p=0.09$, *n.s.*); Fear: ($U=84.5$, $Z=0.53$, $p=0.63$, *n.s.*, $F_{(1,25)}=0.00$, $MSE=1.89$, $p=0.99$, *n.s.*); Happiness: ($U=70.5$, $Z=-1.18$, $p=0.24$, *n.s.*, $F_{(1,25)}=1.61$, $MSE=6503.3$, $p=0.22$, *n.s.*); Surprise: ($U=85.5$, $Z=0.63$, $p=0.63$, *n.s.*, $F_{(1,25)}=0.15$, $MSE=663$, $p=0.70$, *n.s.*); or Sadness: ($U=88.5$, $Z=0.73$, $p=0.73$, *n.s.*, $F_{(1,25)}=0.43$, $MSE=1177$, $p=0.52$, *n.s.*).

Table 9.2: Face emotional intensity rating

	Controls (n=16)			Epilepsy (n=12)			Significance
	Mean	SD	*Range %	Mean	SD	*Range %	sig.*
Anger	-61.0	(82.0)	-280 – 24	-38.42	(52.1)	-157 – 23	$p=0.92, n.s.$
Disgust	-94.5	(53.9)	-240 – -3	-67.4	(52.0)	-155 – 24	$p=0.09, n.s.$
Fear	-12.25	(95.9)	-280 – 136	3.25	(56.3)	-156 – 68	$p=0.99, n.s.$
Happiness	64.38	(67.4)	-260 – 7	-30.2	(54.6)	-120 – 57	$p=0.22, n.s.$
Surprise	-74.7	(72.1)	-280 – 15	-55.7	(56.2)	-66 – 50	$p=0.70, n.s.$
Sadness	-82.9	(49.1)	-220 – 2	-66.9	(54.2)	-139 – 52	$p=0.52, n.s.$
Total	-389.7	(380.0)	-1,560 – 120	-255.9	(265.9)	-778 – 200	$p=0.49, n.s.$

* Analysis of Covariance, data lacks normal distribution

** Range=% of variation

Emotion Recognition Score, Easy or Hard

Analysis explored group differences to determine whether the epilepsy group had specific deficits on either easy or hard to identify stimuli. Stimuli were rated as ‘easy to identify’ [80% and 100%] or ‘hard to identify’ [20% and 40%] by removing the stimuli closest to the mean [60%] and omitting neutral [0%]. Only ratings for correct scores were included. Kolmogorov-Smirnov test revealed non-normal distribution and Levene’s test revealed a lack of homogeneity. The Mann-Whitney U test and ANCOVA controlling for age revealed no significant difference between groups for Easy to identify stimuli ($U=92.5$, $Z=-0.17$, $p=0.90$, $n.s.$, $F_{(1,25)}=0.00$, $MSE=2.96$, $p=1.00$, $n.s.$); or for Hard to identify stimuli ($U=77.0$, $Z=-0.90$, $p=0.39$, $n.s.$, $F_{(1,25)}=1.19$, $MSE=3.58$, $p=0.29$, $n.s.$).

Years of Epilepsy

Pearson’s correlation coefficient explored the relationship between ‘years of epilepsy’ and FER, [$n=11$, missing $n=1$]. The analysis was approaching a significant positive relationship for correct emotion identification, $r=-0.43$, $p=0.091$ (*one-tailed*) $n.s.$, and non-significant for accurate emotion intensity rating, $r=0.15$, $p=0.33$ (*one-tailed*).

9.1.5 Discussion

This experiment explored facial emotion recognition and emotion recognition intensity in adults with and without epilepsy. The results show that there is no difference in FER between groups. ‘Years of epilepsy’ were approaching significance for emotion identification but not emotion intensity rating, with participants who have recent onset scoring lower than participants with chronic epilepsy. The null hypothesis cannot be rejected, as no difference in FER was demonstrated.

The aim of this study was to explore FER as a measure of amygdala functioning for somatic marker formation. As the null hypothesis cannot be rejected, this implies that evidence for a dysfunctional amygdala was not found in this experiment. As the mean duration of epilepsy was 18 years, these results would be inconsistent with amygdala damage in chronic epilepsy which implicates impaired FER to the extent of amygdala damage (Adolphs, 2001). Amygdala damage leads to impairments of the emotional feedback processes revealing that the amygdala is a critical structure for somatic state activation. Bilateral amygdala damage patients do not generate SCR's and perform worse than vmPFC damage patients (Bechara et al., 1999). However, the evidence for unilateral amygdala damage is inconsistent (eg. Adolphs et al., 1994; Fowler et al., 2006). Chapter 10 discusses the results of Experiment 6 and the implications for somatic marker formation.

There may be several reasons why this experiment has not found any deficit of FER in the epilepsy group. First, performance may be influenced by gender differences, as females outweighed males in this experiment [M:F, 1:3], whereas the research in adults with ASD are mostly or entirely male participants (eg. Ashwin et al., 2006). Second, previous research has shown that early onset TLE has been related to a deficit of FER for fearful expressions whereas late onset TLE has not been related to a deficit of FER (McClelland, Garcia, & Peraza, 2006). Third, AEDs are known to improve socio-emotional functioning and therefore face emotion recognition may be impacted upon by AEDs, masking a genuine difference (Di Martino & Tuchman, 2001). Addressing each point in turn, the first explanation suggests that the difference in FER is predominantly demonstrated by research of males rather than females with ASD, while several studies with ASD females lack comparisons with matched control females (eg. Harms et al., 2010). However some studies have demonstrated that females with AS perform worse on FER than matched controls such as Golan and colleagues, although these results are based on comparisons between 6 females with ASD and 5 age and IQ matched controls (Golan et al., 2006). However, in support of an affective deficit in females with ASD, a recent study of 33 males and 29 females found that males and females do not differ on self-reported empathy measured employing the Empathy Quotient [EQ] as a broader measure of basic emotional ability (Lai et al., 2011). This supports an early study employing the EQ of 65 males and 25 females with AS or HFA which suggests a more general impairment in identifying complex emotions (Baron-Cohen & Wheelwright, 2004). To date, no research has been conducted with broader measures of empathy such as the EQ to assess adults with epilepsy. In TLE, FER deficits have been related to and early insult and right medial temporal structures, and male gender has been related to both early-onset and right hemispheric epilepsy (Meletti et al., 2009; Doherty et al., 2003; Hlobil et al., 2008).

The second explanation suggests that as the participant sample had more late onset than early onset epilepsy adults with TLE, age at onset was the key factor in this experiment for FER performance (McClelland et al., 2006; Meletti et al., 2009). This suggestion may have some value as late onset epilepsy participants [$n=8$] outweighed early onset participants [$n=3$]. It should be remembered that individuals with adulthood-onset of epilepsy are likely to have normal childhood development of FER ability. Any loss to this ability may be due to impact of the initial seizures on the amygdala, and any recovery to the amygdala may be influenced by seizure frequency and duration. The impact of the negative effects of epilepsy onset, sometimes referred to as the ‘initial hit’, and FER have not been well researched. The trend towards participants with recent onset epilepsy scoring lower than participants with chronic epilepsy for FER accuracy suggests this might be a valuable line of enquiry in those with adulthood-onset of epilepsy. However, contradictory findings have suggested that age at onset of epilepsy is not a factor for impaired fear recognition in adults so clearly other factors have yet to be identified (Reynders., 2005). Meletti and colleagues demonstrated that chronic drug-resistant TLE may be a factor for FER (Meletti et al., 2009). As onset and AED control were not analysed, the influence of these factors on performance in this experiment is unknown. The third explanation suggests that AEDs, known to affect social and emotional processing, may mask a difference in FER ability. Given that a FER deficit is found in those with chronic drug-resistant TLE and that AED control correlated with social responsivity scores in Experiment 3 in a large group of adults with epilepsy, AEDs may be a factor for performance in this task. This would be consistent with the evidence that AEDs improve autistic characteristics and the notion that AEDs mask these characteristics in adults with epilepsy. Epileptic activity is related to progressive changes in functional organisation of the MTL. It was found that FER accuracy was approaching a significant positive relationship with ‘years of epilepsy’. However, the lack of a significant negative relationship here is inconsistent with evidence that patients with chronic MTLE show deficits in the recognition of both facial and vocal expression of emotions, or with previous evidence that a deficit of FER is associated with duration of epilepsy (Bonora et al., 2011; Meletti et al., 2009).

A deficit in FER has previously been demonstrated to be widespread across epilepsy types and not confined to TLE alone. However, these results demonstrate that adults with epilepsy can demonstrate intact FER ability. Taken together with evidence from previous research, this suggests that FER ability in adults with epilepsy can be influenced by multiple factors such as gender, onset, and AED control, and the small sample size in this experiment limited any analysis of these factors. In addition, the epilepsy sample may reflect a sampling bias of well-functioning adults with epilepsy. Of note, a review of the literature of FER studies for all ages of children, adolescents and high-functioning adults with ASD has recently been highlighted as inconsistent and contradictory (Harms et al., 2010). Generally, the researchers conclude that as a whole, FER behavioural studies are only slightly more

likely to find a deficit of FER in ASD than not. Taken together, the mixed findings of FER ability in ASD and the multiple factors influencing mixed findings of FER ability in epilepsy reveal a spectrum of varying levels of ability or deficit of FER within each condition.

Limitations

This experiment is limited by the sample size. Previous research highlights FER impairments in patients with mTLE, right TLE and chronic TLE. This experiment would have benefitted from analysis of childhood/adulthood-onset epilepsy.

Summary

The results reveal that there was no difference in FER between adults with and without epilepsy, suggesting that the ability to recognise facial emotion expressions was intact. From this experiment, it can be inferred that amygdala function was not significantly impaired in adults with epilepsy, and is not a significant negative factor for somatic marker formation. Further studies of FER would benefit from exploring the effect of AEDs. In addition, a broader measure of empathising ability employing the EQ could be a potential line of enquiry for future research.

9.2 Experiment 7: IOWA Gambling Task [IGT]

9.2.1 Background

Experiment 7 investigates decision making abilities in adults with epilepsy, to explore whether there is a relationship between decision making and the formation of somatic markers. Consistent with this theory, Temporal lobe epilepsy [TLE] has been associated with impairments in temporal and frontal lobes, and more recently in the pre-frontal cortex. Research suggests that those with TLE have lower connectivity to brain regions outside the temporal lobe structures, such as the medial prefrontal cortex and other extratemporal regions, where no abnormal EEG activity is detected (Laufs et al., 2007). This may result from activity in the limbic system which is tightly connected to the prefrontal cortex.

Research suggests that adults with ASDs may experience and demonstrate decision making difficulties. Luke, Clare, Ring, Redley, and Watson (2011) showed that adults with ASDs self-reported experiencing more everyday life decision making difficulties than adults without ASDs, using a novel questionnaire. Decision making in adults with ASDs was associated with a delay in reaching a choice, a tendency to avoid decision-making, and associated anxiety, exhaustion, and difficulties engaging in the process. The researchers state that their findings highlight latency of decision-making and levels of

arousal in decision-making as important areas of potential research, which may benefit those with ASDs. In 2006, Johnson and colleagues assessed adolescents and young adults with ASD on decision making under ambiguity, employing the IGT (Johnson, Yechiam, Murphy, Queller, & Stout, 2006). They examined patterns of learning in relation to the Expectancy-Valence Learning model. The researchers found that while individuals with AS did not differ in proportions of advantageous deck selection from the control group, they showed a distinct pattern of frequent shifts between all four decks, rather than a clear deck preference. They suggest that those with ASD demonstrate pattern of continuous switching by continually shifting between the deck alternative options. Yechiam and colleagues argue that this learning style relies on convergent thinking which may offer an advantage such as enhanced exploration (Yechiam, Arshavsky, Shamay-Tsoory, Yaniv, & Aharon, 2010). The researchers investigated IGT performance of adolescents with ASD revealing that they appear to sample more from the whole range of decks throughout the task compared to the control group, which did not impair overall performance. They found that although the ASD group were unaffected by previous losses in their switching decisions, they revealed a pattern of high deck switching throughout the task compared with the control group. The researchers suggest that these individuals have a unique learning style influenced by the exploratory value of their choices (Yechiam et al., 2010). Yechiam and colleagues suggest that this learning style relies on convergent thinking and offers three explanations for this pattern. When the researchers modelled this into basic components, their results suggested that the model favoured the third explanation: an increase in exploration, where exploration is not random, but is extensively driven, and may offer an advantage. However, this explanation is limited as it contradicts with evidence of other autistic characteristics such as restricted and repetitive behaviours. Further, one implication of such an approach is that there is no benefit for this advantageous exploratory learning style as there is no improvement in decision making ability. In addition, the model does not take into account the ‘cost’ of impaired social cognitive abilities compared to the ‘benefit’ of enhanced exploration and for some individuals with ASD, social difficulties are a cause for concern.

Experiment 7 will be conducted by employing a computer based version of the IGT to assess decision making. This task requires participants to select cards from four decks displayed on-screen in order to perform a card selection which will result in the accumulation of as much ‘digital money’ as possible (Bechara et al., 1994). The task outcome and deck strategies will be evaluated between groups. This allows investigation into the exploratory power of the SMH in relation to the vmPFC, and seeks specific impairments in decision making abilities in adults with epilepsy.

9.2.2 Aim

This experiment investigates decision making abilities in adults with epilepsy to explore whether there is a relationship between decision making and the formation of somatic markers. The IGT is a measure of decision making, and requires learning guided by somatic markers of the consequences of decisions, provided as reward and punishment contingencies preceding explicit insight. It measures the ability to learn from previous outcomes and incorporate this knowledge into a decision making framework. The aim is to make as much hypothetical money as possible. Successful social interaction depends on representations of internal somatic states, emotion-based biasing signals, which play a major role in social cognition. The vmPFC has been implicated in the integration of somatic markers, and recent evidence has demonstrated lasting alterations in the structure and functioning of the PFC resulting from early-life seizures (Kleen et al., 2011). Damage to the ventromedial region of the PFC can result in an inability to experience somatic states (Bechara, Damasio, Tranel, & Damasio, 2005). Consistent with the SMH, damage to the vmPFC disrupts social behaviour profoundly, because while social cognition is preserved, patients inability to process the emotional component results in a lack of engagement of complex social emotions, inappropriate affect, and social withdrawal (Bechara & Damasio, 2000; Farrant et al., 2005).

According to Helmstaedter, the negative effects of chronic TLE on declarative memory can be worse than the semantic impairment caused by disruption of TLE to semantic networks (Helmstaedter, 2002; Helmstaedter et al., 1997). This is important, as Gupta and colleagues argue that the declarative memory system plays a significant role in complex-decision making (Gupta et al., 2009). They argue that declarative memory impairments result in poor integration of the information needed to track the integrated relationships in the IGT. Intact declarative memory, and specifically explicit memory, is crucial for the formation of somatic markers in complex decision making (ibid.). This suggests that for adults with chronic epilepsy, impaired declarative memory may hinder somatic marker formation.

The aim of Experiment 7 is to investigate decision making in adults with epilepsy, to provide a measure for somatic marker formation. This will examine whether compromised somatic marker formation in adults with epilepsy may explain impairments in the social domain which were revealed in the initial experiments. It is hypothesised that adults with epilepsy will demonstrate impaired decision making compared to adults without epilepsy. Performance on this task will provide an understanding about the formation of somatic markers.

Hypothesis

H1: There will be a difference between adults with and without epilepsy in decision making, measured by the IOWA Gambling Task (IGT). Adults with epilepsy will demonstrate poorer decision making abilities compared to adults without epilepsy.

9.2.3 Method

9.2.3.1 Participants

The participant group comprised $n=28$. Data were examined for outliers and atypical patterns, the exclusion of one participant (see data exclusion) resulted in $n=27$: Control Group $n=16$ [Female $n=12$, Male $n=4$], Epilepsy $n=11$ [Female $n=9$; Male $n=2$].

9.2.3.2 Materials

This task employed: 'Bechara's Gambling Task', Psychology Experiment Building Language [PEBL] version 0.11, <http://pebl.sourceforge.net/battery.html>, accessed 2010. This program was displayed on standard 36cm x 28cm monitors.

The IOWA Gambling Task (IGT)

The IGT is a neuropsychological behavioural measure of decision making. It was originally developed by Bechara, Damasio, Damasio and Anderson (1994) to assess individuals with vmPFC damage. It comprises of 4 decks of cards presented face down, each card representing a hypothetical monetary gain across 100 trials. Two decks are disadvantageous with high rewards and high losses over time; two decks are advantageous with low rewards and low losses overtime. The deck is constructed so that selection from advantageous decks will lead to higher monetary outcomes. The risk associated with each selection is unknown and ambiguous. Typically however, healthy controls learn the contingencies of each deck selection and switch to advantageous deck selection as the task progresses. The IGT is considered appropriate to assess many clinical populations. The computerised version of the original paper version is commonly used, without difference between the versions (Bowman et al., 2005). While evidence for reliability of the IGT is lacking, validity is good and performance on the IGT are consistent with the SMH (Buelow & Suhr, 2009).

Validity

The IGT is designed to simulate playing a game in which no 'real money' is used, but in which participants are instructed to win as much fictitious money as possible, and to minimise any losses. According to Bechara and colleagues, participants need to engage in the IGT by generating the same somatic responses that they would do in a real-life situation in order to assess whether poor decision making is the consequence of the participants' inability to experience the emotional attributes of the

experiment (Bechara et al., 1999). Therefore, the researcher explicitly instructed all participants to play the game as though it were with 'real' money, to ensure good validity.

9.2.3.3 Design

The experiment was conducted as a between-groups design. The IV was group: i) Epilepsy, ii) no Epilepsy. The DV were amounts of total money accumulated, the number of advantageous cards selected, and response time [RT] in milliseconds.

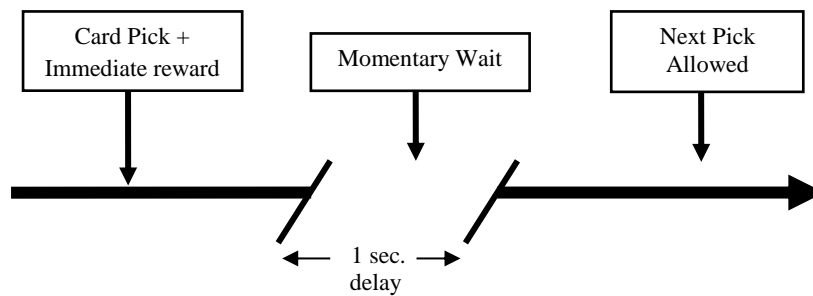
Score, Response Time, Deck Selection

The task will be measured by total score: total money earned during task, measured in dollars (\$000's); response time: measured in milliseconds. In addition, advantageous / disadvantageous deck selection preferences will be explored. Response time for the first selection [RT1] was eliminated as the researcher used this time to explain the display screen features to participants. However, since the first deck selection is the participant's first choice, there is no consideration to be made based on previous selection and removing RT1 did not affect the aim of measuring response time. Therefore participants' RT was measured from RT2-RT100. One solution in future could be to include practice trials. There was no missing data.

Data exclusion

Raw data was checked for evidence of atypical patterns, such as single choice repetitions and responses faster than one second. Epilepsy participant #204 was eliminated as the response time per choice (milliseconds) revealed that the participant responded too quickly in the last 4 blocks, and exceptionally fast in the last 2 blocks of the task. The data revealed that 41 responses by participant #204 were less than half a second (0:00-0:35 seconds), revealing that the response key was pressed almost immediately. Of the fastest responses, 45 responses were quicker than 1:06 seconds, faster than the quickest response time by any other participant. Therefore participant #204 key pressed faster than any other participant for nearly half of the task, showing that participant #204 did not have time to think about the contingencies of each choice. This resulted in the fastest average time per selection of 1:134 seconds (see Table 9.4 for mean RT by group). One explanation for this could be that due to impulsive behaviour, this participant attended to the measure bar which reveals total money earned, rather than the money earned per choice. This may highlight a design limitation of the IGT software employed. One solution could be to integrate a one-second delay, so that each participant must attend to the results of their choices and take account of feedback from each choice, before proceeding, see Figure 9.3.

Figure 9.3: Possible PEBL IGT improvements to eliminate avoidance of attending to previous choice results



9.2.3.4 Procedure

Participants were presented with a computerised version of the IGT showing four decks of cards face down, and \$2000 capital gain of ‘play’ money. Participants were verbally read the standard instructions, and were asked to select cards with the aim of making as much money as possible, or to minimise losses (Appendix N). Participants were informed that decks can be either advantageous or disadvantageous. The researcher pointed to the display screen features while instructions were read out. Participants were asked to play the game as though they were actually accumulating money. No participant was informed that their response time was measured as part of the experimental design. All participants were provided with an opportunity to ask questions before starting. The task comprised of 100 trials lasting 5-10 minutes.

Experimental Observations

In contrast to control participants, the participants with epilepsy were observed to show impulsivity while being read the instructions. Four participants attempted to start the task before the instructions were read. They were prevented from starting until all the instructions were read out, however one participant started the task which was re-set, and this participant [#204] was later eliminated.

9.2.3.5 Ethical Considerations

Ethical considerations have been outlined previously and participants were informed of the task aims (section 8.1.2).

9.2.4 Results

The following analyses were conducted with an independent t-test, and an ANCOVA with age as a covariate to control for group age differences.

Score

An independent t-test explored group differences for score. Kolmogorov-Smirnov test revealed normal distribution ($p>.05$), and Levene's test confirmed homogeneity of variance ($p>.05$). There was no significant difference between group ($t=-0.66$, $df=25$, $p=0.52$, *n.s.*; $F_{(1,24)}=0.94$, $MSE=30.8$, $p=0.34$, *n.s.*), see Table 9.4.

Response Time

An independent t-test explored group differences for average time (T2-T100). Kolmogorov-Smirnov test revealed normal distribution ($p>.05$), and Levene's test confirmed homogeneity of variance ($p>.05$). Time was approaching significance, however when age was controlled for, there was no significant difference ($t=-1.96$, $df=25$, $p=0.062$, *n.s.*; $F_{(1,24)}=0.80$, $MSE=25.76$, $p=0.38$, *n.s.*), see Table 9.4.

Table 9.4: IOWA Task, Total Mean Score and Mean RT by group

	Total Score \$			Response Time per choice (secs.)		
	Mean	(SD)	Range	Mean	(SD)	Range
Controls $n=16$	1746.9	(499)	950-2625	1:584	(0:491)	0:727 – 2:810
Epilepsy $n=11$	1881.8	(564)	850-2525	2:042	(0:728)	1:101 – 3:371

The analysis showed that there was no overall difference in performance between groups for total money accumulated or RT. Further analysis will explore decision making choices for each block in the task.

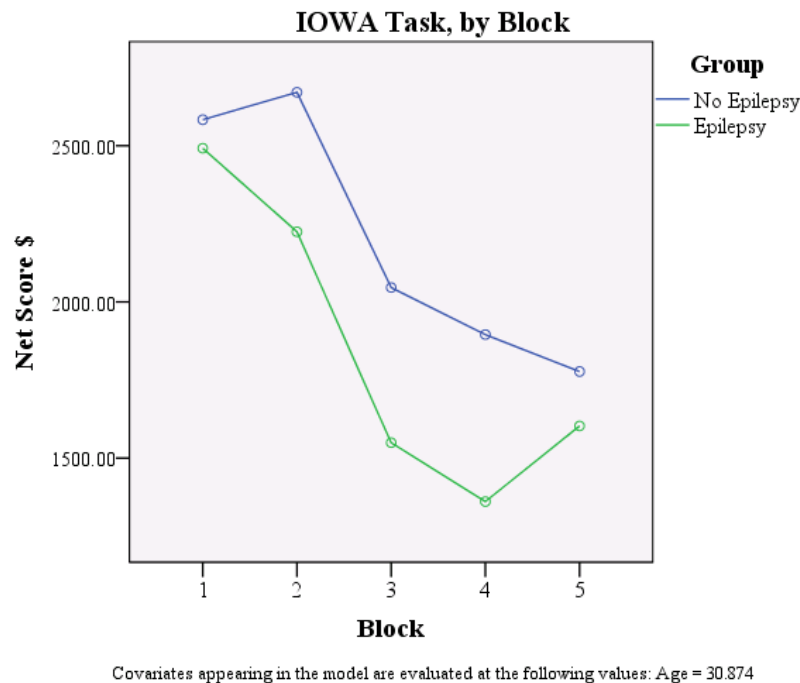
Deck Selection

Score

A mixed design ANCOVA (Group,2 x Block,5) with block as a repeated measure and age as a covariate explored score differences between groups. Maunchly's test for sphericity reveals sphericity is assumed ($p=0.146$). ANCOVA showed a significant main effect for Block ($F_{(4,96)}=5.22$, $MSE=483810$, $p=0.001$), a significant main effect for Group ($F_{(1,24)}=7.83$, $MSE=15304$, $p=0.010$), and a non-significant trend for the interaction of block and group ($F_{(4,96)}=2.21$, $MSE=204990$, $p=0.073$).

Post-hoc ANCOVA analysis for each block with age as a covariate revealed that deck choice was not significantly affected by Group for Block 1 ($F_{(1,24)}=2.24$, $MSE=41828$, $p=0.133$); significant for Block 2 ($F_{(1,24)}=4.46$, $MSE=1004570$, $p=0.045$); significant for Block 3 ($F_{(1,24)}=5.89$, $MSE=1242397$, $p=0.023$); significant for Block 4 ($F_{(1,24)}=7.90$, $MSE=1437960$, $p=0.010$); and non-significant for Block 5 ($F_{(1,24)}=1.21$, $MSE=152463$, $p=0.283$), see Figure 9.5.

Figure 9.5: Group Performance on the Iowa gambling task, measured by mean net scores selected for each of 5 blocks, of 20 cards.



*Note: the Net Score is the score which varies from the \$2,000 at start.

Time

A mixed design ANCOVA (Group, 2 x Block, 5) with block as a repeated measure and age as a covariate explored time differences between groups. Mauchly's test for sphericity reveals sphericity is violated ($p=.001$), therefore values reported are corrected by a conservative correction factor applied to the degrees of freedom used, Greenhouse-Geisser correction. ANCOVA showed no significant main effects for Block ($F_{(1,24)}=1.35$, $MSE = 3.03$, $p=0.268$), there were no significant main effects for Group ($F_{(1,24)}=0.79$, $MSE = 1.03$, $p=0.380$), and the interaction of block and group was not significant ($F_{(1,24)}=1.66$, $MSE = 3.70$, $p=0.20$).

These results indicate that while there was no difference between group performance for RT, there was a significant effect for block between the groups. However, these results do not indicate whether selection performance of adults with epilepsy differed to adults without epilepsy for advantageous decision making, so further investigation explored group differences and advantageous deck selection.

Advantageous and Disadvantageous Deck Selection

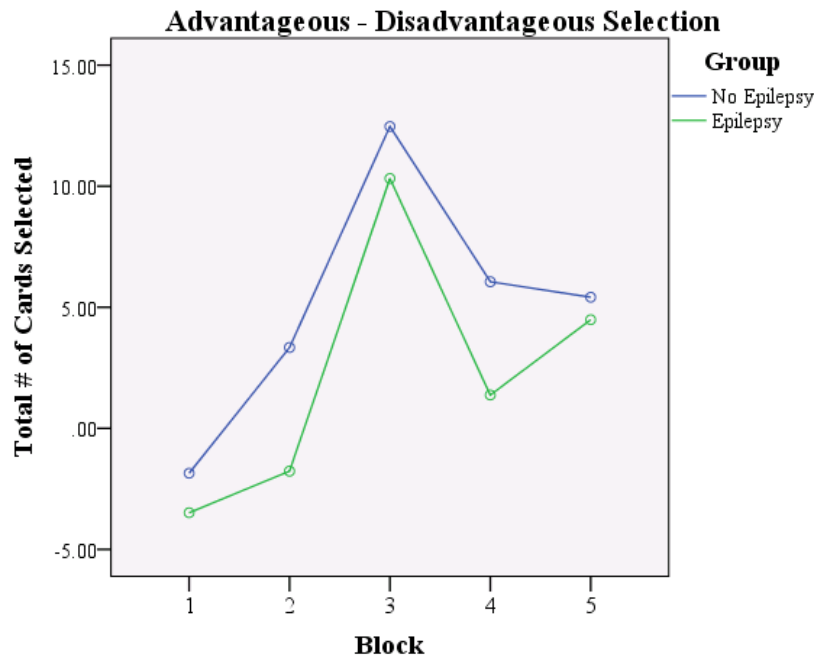
Analysis was conducted to explore group differences in advantageous and disadvantageous deck selection, to reveal the extent to which participants learn to select advantageous decks at a higher rate than disadvantageous decks as the task progresses. Decks A and B are disadvantageous with large gains and large punishments resulting in a net \$ loss; decks C and D are advantageous with small gains and small punishments resulting in a net \$ gain.

Deck Selection

The mean advantageous/ disadvantageous [A/D] score was calculated by subtracting the number of disadvantageous deck selections (decks A and B) from the number of advantageous deck selections (decks C and D). A higher score indicated that deck selections were more advantageous. A mixed design ANCOVA (Group, 2 x Block, 5) with block as a repeated measure and age as a covariate explored time differences between groups. Mauchly's test for sphericity reveals sphericity is violated ($p=.003$), therefore values reported are corrected by a conservative correction factor applied to the degrees of freedom used, Greenhouse-Geisser correction. ANCOVA showed no significant main effects for Block ($F_{(4,96)}=0.92$, $MSE = 26.6$, $p=0.431$), there was a significant main effect for Group ($F_{(1,24)}=4.45$, $MSE = 42.3$, $p=0.046$), and the interaction of block and group was not significant ($F_{(4,96)}=0.864$, $MSE = 24.9$, $p=0.46$).

Post-hoc ANCOVA analysis for each block with age as a covariate revealed that deck choice was not significantly different for Group in Block 1 ($F_{(1,24)}=0.44$, $MSE=13.4$, $p=0.512$); significant for Block 2 ($F_{(1,24)}=6.34$, $MSE=131$, $p=0.019$); approaching significance for Block 3 ($F_{(1,24)}=3.54$, $MSE=23.0$, $p=0.072$); approaching significance for Block 4 ($F_{(1,24)}=3.29$, $MSE=110$, $p=0.082$); and not significant for Block 5 ($F_{(1,24)}=0.113$, $MSE=4.36$, $p=0.74$), see Figure 9.6.

Figure 9.6: Mean number of cards selected from the advantageous minus disadvantageous decks for each of 5 blocks of 20 cards between adults with and without epilepsy.



Covariates appearing in the model are evaluated at the following values: Age = 30.874

Overall, the groups performed significantly different, and trends towards these differences throughout the task can be seen in figure 9.6. Figure 9.7 below shows the pattern of group differences by individual decks for each group.

Figure 9.7: Deck selection from each of 4 decks [A,B,C & D] as a percentage of total selection, for each of 5 blocks of 20 cards.

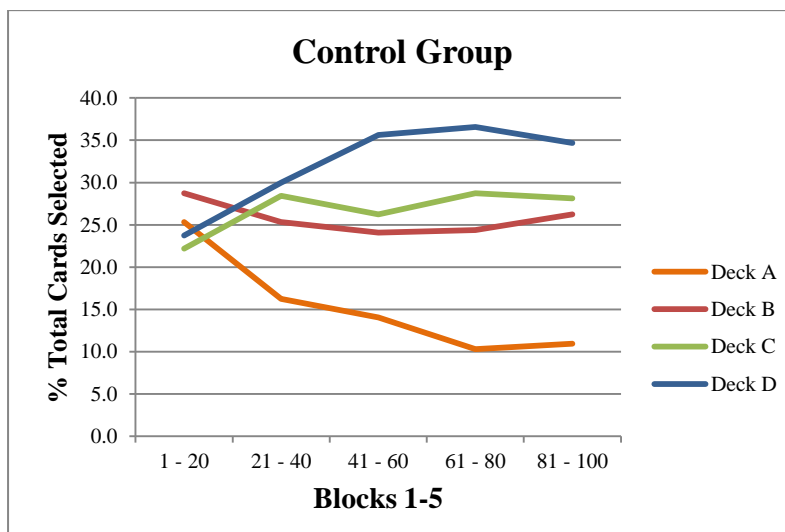
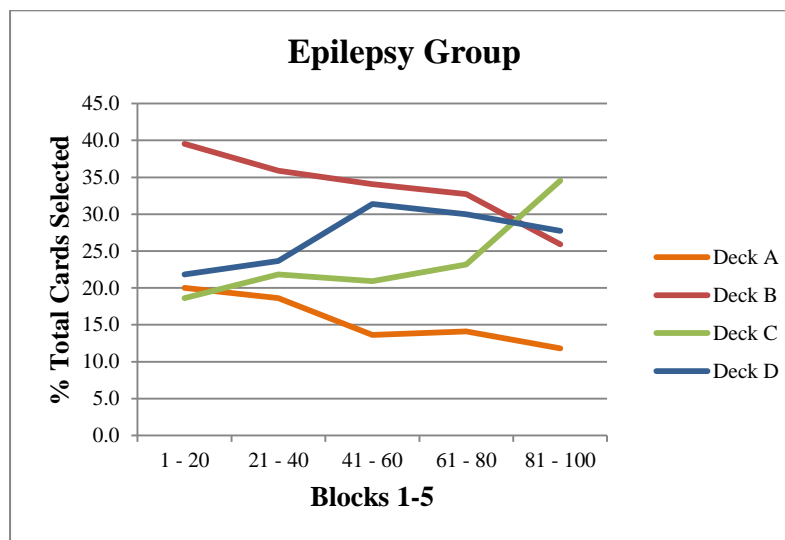


Figure 9.7: Deck selection from each of 4 decks [A,B,C & D] as a percentage of total selection, for each of 5 blocks of 20 cards.



Years of Epilepsy

Participants with epilepsy reported the time since epilepsy diagnosis in years and months (Mean=18.1, std. dev.=12.8, min=4.0, max=43.0). A Pearson's correlation coefficient revealed no significant differences in score, $r=.147$, $p=.34$ (one-tailed), *n.s.* However, there was a significant difference for time, participants with more 'years of epilepsy' took longer to complete the task than those with fewer years, $r=.636$, $p=.031$ (one-tailed). A Pearson's correlation was conducted to explore 'years of epilepsy' and advantageous/disadvantageous deck selection (see Deck Selection above for how the A/D score was calculated). The score was approaching significance, with a trend for adults with recent epilepsy onset revealing a higher mean A/D score as they selected more cards from advantageous decks, $r=-.546$, $p=.051$ (one-tailed), *n.s.*

The task comprised of 5 blocks, and post-hoc analysis revealed a significant difference for choosing less advantageous than disadvantageous cards in block 2 at the beginning. This was followed by a non-significant trend in blocks 3 and 4 towards less advantageous decision making. Interestingly though, while adults with epilepsy selected fewer advantageous than disadvantageous cards in blocks 2 to 4, block 5 revealed a sudden increase in advantageous card selection. This pattern can be compared to group differences in deck selection. While the Control group shows a clear preference for advantageous Decks C and D than Decks A and B by block 2, the epilepsy group demonstrated this pattern at block 5, see Figure 9.7. This suggests the control group initially selected from disadvantageous decks A & B, but by block 2 they had learned to avoid the bad decks and choose the good decks. Therefore, the control group showed evidence of learning demonstrated by the

predominance of advantageous over disadvantageous choices. Figure 9.7 shows that while control groups in other studies show a learning effect which may be more advantageous, in this experiment the control group selected advantageous choices mainly from decks C and D which have less frequent minor punishments. Selection from deck B rather than deck C can reduce overall winnings. Yet the control group demonstrated that throughout the task, they selected more from the advantageous D deck which is their main choice. Like disadvantageous deck B, deck D has high frequency gain and low frequency loss, but as an advantageous deck it is the best choice for a winning strategy. Consequently with this selection, the control group showed learning.

9.2.5 Discussion

The aim of this experiment was to explore decision making in adults with and without epilepsy. The results showed that adults with epilepsy demonstrated poorer decision making abilities compared to adults without epilepsy. They selected fewer advantageous cards throughout the task as evidenced by the significant group differences in advantageous minus disadvantageous deck selection, and also demonstrated significant differences in selection between the four decks. However, there were no significant group differences for time taken to complete the task. Therefore the null hypothesis can be rejected as decision making was found to be significantly different between groups, and the experimental hypothesis H1 can be accepted.

The difficulties associated with investigating learning behaviours on the IGT by comparing data with variability in the control group has been criticised by Dunn and colleagues (2006), who state that it is necessary to look at objective criteria such as advantageous deck selection relative to chance levels as well as comparisons with a control group. Therefore, Figure 9.7 provides a percentage of total cards selected by block. By comparison, the epilepsy group did not show they had learned to avoid the bad decks towards the end of block 4. By block 5, the epilepsy group show a delayed shift to a learning strategy and avoided the bad decks. This pattern of shifting reveals a slower learning effect with a fairly consistent selection trend from deck B in association with increased selection from decks C and D. A decrease in selection from disadvantageous deck A occurs in later blocks than for the control group. In addition, the epilepsy group appear to sample more from the whole range of decks throughout the task compared to control group who seem to select mostly from decks C and D, and from deck B selections as discussed, for a review on deck B selection in normal subjects see Lin and colleagues (Lin, Chiu, Lee, & Hsieh, 2007).

Impaired decision making abilities implicates vmPFC functioning and has been specifically linked to patients with vmPFC lesions who demonstrate an inability to reverse a previously learned contingency

(Mah et al., 2005). Decision making is supported by the mesial temporal lobes, and impaired decision making is found in adults with mTLE (Bonatti et al., 2009). Evidence of impaired decision making on the IGT was found in adults with mTLE, even after surgery (Bonatti et al., 2009). These adults demonstrated frequent shifts between advantageous and disadvantageous decks which was significantly different to controls (Bonatti et al., 2009). Bonatti and colleagues suggested that frequent deck selection was random, as they could not specifically profit by selecting advantageous decks after negative feedback. The researchers found no difference between right and left TLE patients, and concluded that integrity of both medial temporal lobe circuits are related to advantageous decision making on the IGT. When the mTLE patients did perform advantageous decision making, Bonatti suggests that they may be compensating for emotional processing difficulties by using other cognitive resources such as explicit knowledge of probabilities. Neuroimaging has identified lower connectivity in the vmPFC in TLE and associated this with unilateral hippocampal damage (Frings et al., 2009). These findings are consistent with performance of patients with TLE who usually present with unilateral hippocampal damage which is related to disadvantageous decision making on the IGT (Labudda, Frigge, & Horstmann, 2009). Crucially, hippocampal damage is caused by seizures in TLE which may have negative consequences for decision making abilities (Salmenperä, Kalviainen, Partanen, & Pitkänen, 1998).

However, Laufs and colleagues employed fMRI to demonstrate that interictal epileptic discharge propagation occurs to the medial frontal brain regions between seizures which may have behavioural implications (Laufs et al., 2007). Laufs and colleagues demonstrate that IEDs affect brain activity between seizures, and found distinct patterns of activation in the medial frontal brain regions in patients with focal epilepsy which was not TLE, which may have functional consequences resulting from the IEDs. Given the importance of the vmPFC for integrating and organising information necessary for somatic markers, this evidence suggests that more than one epilepsy type may be related to vmPFC functional differences. Impairment on the IOWA task is also consistent with evidence of vmPFC lesion patients who have difficulties in their social life (Reimann & Bechara, 2010). This can be compared to adults with epilepsy who demonstrated impairment on the IOWA task and self-reported social difficulties. Recent evidence has identified that early-life seizures in animal studies can result in lasting alterations in the structure and functioning of the PFC (Kleen et al., 2011). The researchers state that these early seizures result in thicker prelimbic PFC which are consistent with the abnormal and increased brain growth associated with ASD. From their findings, the researchers identified that further research is needed to investigate whether underconnectivity in autism is related to the underconnectivity between the hippocampus and PFC after early-life seizures have occurred. Importantly, this recent evidence of abnormal functioning in the PFC would be consistent with impaired decision making for adults with childhood-onset of epilepsy.

The discussion above suggests that there may be a deficit of formation of somatic markers in adults with epilepsy which results in significant differences in decision making which may be consistent with either functional differences or functional connectivity to the medial and ventromedial sectors.

This discussion explores three explanations for this pattern of performance: firstly delayed formation of associations for somatic markers; secondly weakened formation of associations, and third, failure to link associations after encoding information.

The first explanation is delayed formation of associations for somatic markers due to differences in encoding information. This explanation would lead to a pattern of learning which may be identical to the control group, but occurring at a later time point. However the pattern of learning by the epilepsy group in block 5 is not identical and there does not appear to be a delay by the end of the task. In this experiment, there are fewer previous experiences to draw upon at the beginning of the task in block 1. The data suggests that the epilepsy group are delayed from block 1 at the early stage but not the later stage of the task. Figure 9.6 plots the advantageous minus disadvantageous deck selection, revealing that the epilepsy group demonstrate fewer advantageous selections throughout the task, but this is worse in block 2 which would be consistent with a delay in the beginning. In support of a delay in learning, the RT data reveals a behavioural change towards advantageous deck selection in the control group was reached at the end of block 1 at mean time of 25.4 seconds, whereas this change was reached by the epilepsy group at the end of block 4 at a mean time of 1 minute and 26.6 seconds. However, an explanation that the adults with epilepsy have a general delay in somatic marker formation does not provide an explanation for the sudden learning pattern in block 5. Therefore this does not provide a complete explanation since delayed formation is not shown at the end.

The second explanation is that probabilistic contingencies are not being fully encoded, the resulting upstream effect may be revealed through a weakened formation of somatic markers. Formation of weaker associations may be related to a weakened connection between the amygdala and hippocampus. The strength of the connection between the amygdala and hippocampus is predictive for adaptive learning (Yechiam et al., 2010). However, if formation of somatic markers were weakened, then performance in blocks 1 and 5 would show similar patterns overall to the control group. However, in block 5 the epilepsy group show an increase in performance that is not consistent with this explanation, therefore this explanation is rejected.

The third explanation proposes that participants with epilepsy encode all information but fail to link associations into meaningful reward/punishment categories immediately, however they store all information until they form the associations, subsequently profiting from this later in the task. This explanation suggests that information is encoded, but that formation is hindered, possibly due to functional differences in the vmPFC, resulting in a loss of linking the physiological response to the stimulus. This could explain the pattern of initial poor performance, but once the associations are linked, the result would be a sudden observable change of improved performance. This is exemplified by fast learning in block 5 in the epilepsy group, in contrast to block 4 where selections are no better than chance. Once linked, these associations are strong enough to drive advantageous decision making quickly, providing an outcome comparable to the control group.

The above evaluation suggests that the adults with epilepsy demonstrated a delay at the beginning which is consistent with a lack of ability to learn contingencies as well as the control group at the outset, and short enhanced improvement at the end which is consistent with linking the associations into meaningful categories to drive advantageous decision making. The contribution of the hippocampus and amygdala to decision making is discussed further in section 10.2.

Previously, individuals with ASD have demonstrated similar proportions of advantageous deck selection to a control group employing the IGT; however they demonstrated more frequent shifts between all four decks, rather than a clear deck preference (Johnson et al, 2006). This is supported by later research demonstrating that adolescents with ASD appear to sample more from the whole range of decks throughout the task compared to the control group, although this did not impair overall performance (Yechiam et al., 2010). Gupta and colleagues suggest that a wide range of sampling in individuals with bilateral hippocampal damage is related to declarative memory impairments which prevent these individuals from updating relational representations between the decks to form the kind of relational information needed to track of their experiences with each deck (Gupta, et al., 2009). In Experiment 7, the control group demonstrated a range of sampling at the beginning of the task which shifted towards block 5, with a clear preference for advantageous decks early in block 2. The epilepsy group did not demonstrate a narrow range of sampling at the beginning, or a clear preference for advantageous decks early in the task. They also demonstrated significantly fewer advantageous deck selections in one of the blocks. However, both adults with epilepsy and adults with ASD have demonstrated that overall performance on the IGT measured by total \$ net at T100 was not impaired.

Limitation

There are several limitations of this experiment. The experiment was limited by sample size and sample bias. It is unknown whether performance was influenced by depressive symptoms which are common in TLE (Kanner & Balabanov, 2002). Further, AEDs are related to a decline in performance IQ, concentration and mental speed, and one AED type can impair complex decision making (Cavanna, 2010). It is unknown whether participants in the 'AEDs unknown, $n=4$ ' group were treated with this AED type. It is also unknown whether lateralisation influenced performance as has been suggested previously, however recent research has suggested it may not be a factor for decision making (Delazer et al., 2010).

Summary

The results reveal that performance during the task was significantly different, with the epilepsy group revealing a pattern of delayed learning, and selection more from a wider range of decks, compared to a matched control group. The findings reveal differences consistent with frequent deck changes in the epilepsy group which are consistent with previous research suggesting that individuals with ASD display frequent deck sampling (Johnson et al., 2006). One suggested explanation is that formation of the relational properties could be hindered; however this deficit might be compensated for by the use of other cognitive resources resulting in differences of performance during the task. The IGT is a reliable behavioural measure, not a measure of brain structural differences, therefore conclusions for the contribution of hippocampus and amygdala to somatic marker formation can only be inferred from Experiments 5 and 6 and will be discussed in Chapter 10. However, findings from Experiment 7 may have implications for social interactions in the social domain underpinning autistic characteristics found in adults with epilepsy. Further research could compare performance of patients with epilepsy on longer trials [>100] on the IGT, to explore whether the short enhanced learning curve toward the end of the task continues to exhibit the same or a different pattern as a control group during the additional trials.

Chapter 10

General Discussion

*“I think that epilepsy can do a lot to inform autism,
I am now realizing that autism is informing us,
potentially a lot, about epilepsy.”*

*Professor Frances Jensen, April 2011
President-elect of the American Epilepsy Society
Harvard Medical School*

This chapter presents an overview of the specific findings of the experiments in relation to the research aim and limitations of this research project. The findings are discussed with reference to the specific theory and previous research. The wider implications of the research are also addressed. Lastly, future research to address findings from this research is suggested.

10.1 Experiment Aim

To my knowledge, this was the first comprehensive exploration of autistic characteristics in adults with epilepsy without a diagnosis of any ASD. The first aim of this experiment was to establish the extent to which autistic characteristics are associated with and without seizure auras in adults with epilepsy. The research employed a new method of psychological assessment that was epilepsy-specific. This was specifically aimed at understanding the extent to which autistic characteristics would be affected by seizure activity. It sought to provide an accurate measure for the range of difficulties suspected in adults with epilepsy. The second aim of the research was to explore the extent to which self-reported social difficulties related to social cognitive ability. To achieve this aim, an empirical measure of decision making was employed to provide a quantitative assessment of social cognitive ability to explore the Somatic Marker Hypothesis, for a theoretical explanation. Face emotion recognition abilities and specific memory patterns related to ASD based on the Task Support Hypothesis were investigated to examine the mechanisms underpinning somatic marker formation.

Table 10.1: Summary of Findings

# Experiment Task	Results (Group)	Results (Conditions)	Significant factors
1. Autism Quotient ($n=78$)	$p=.001$, sig.	$p <.001$, sig.	
2. Intuitive Physics Test ($n=42$)	not significant	$p =.033$, sig.	
Adult Eyes Task-Revised ($n=42$)	not significant	not significant	
3. Social Responsiveness Scale ($n=106$)	$p =.004$, sig.	$p =.005$, sig.	AEDs, Chronic epilepsy
4. Repetitive Behavior Scale-Revised ($n=83$)	$p =.049$, sig.*	not significant	AEDs
5. TSH Relational Memory ($n=27$)	Trend for UWL, not significant		
TSH Encoding & Recall Memory ($n=26$)	not significant		
6. Face Emotion Recognition ($n=28$)	not significant		
7. IOWA task ($n=27$)	$p=.046$, sig.		

* *epilepsy/ex-epilepsy only*

10.2 Findings from Main Experiments

The specific aim of Experiment 1 was to investigate autistic traits in a heterogeneous sample of adults with epilepsy, employing a new method of assessment. Based on the findings of Experiment 1, Experiment 2 specifically aimed to establish that not all autistic characteristics were impaired in adults with epilepsy. To undertake such research, the empathising-systemizing paradigm was investigated. Consistent with findings from Experiments 1 and 2, Experiment 3 investigated reciprocal social interaction in epilepsy, in order to distinguish ASD characteristics from unspecific social and communicative impairments. Having established that adults with epilepsy reported greater autistic characteristics, Experiment 4 investigated another core characteristic of ASD unrelated to social and communication difficulties, restricted and repetitive behaviours. Three of these studies examined the extent of autistic characteristics, while Experiment 2 aimed to establish that not all abilities would be impaired. Based on the common pathology, common genetic basis, high co-morbidity of autism and epilepsy, and poor social adjustment in adults with epilepsy, it was hypothesised that adults with epilepsy would have higher autistic traits and poorer reciprocal social interaction than adults without epilepsy, and that empathising would be impaired while systemizing would be retained. Based on previous literature which correlated severity of autism with ‘sameness’ behaviours, it was hypothesised that adults with epilepsy would reveal increased restricted and repetitive behaviours compared to adults without epilepsy, and these would be greater than ex-epilepsy participants.

These experiments identified the extent of autistic characteristics, and the major findings were that autistic traits and poorer reciprocal social interaction were significantly higher in adults with epilepsy regardless of epilepsy type, while empathising abilities were found to remain intact. These specific autistic characteristics were negatively influenced by seizure activity. The results of Experiment 1 are consistent with previous evidence for differences in four of the five subscales of autistic characteristics in adults with epilepsy. The results of Experiment 3 are consistent with previous evidence of poor psychosocial adjustment and impaired social functioning in adults with epilepsy (McCagh et al., 2009). Seizure-freedom in adulthood did not result in improved reciprocal social interaction. This is inconsistent with previous evidence demonstrating increased social interactions after resolution of epilepsy through surgery (Hamiwka et al., 2011). This is also inconsistent with research that showed seizure-freedom during adolescence was related to improvements of social functioning in adulthood (Lach et al., 2010). It is unknown whether these autistic-like characteristics resolve with seizure-freedom in adulthood. Although previous evidence inferred a possible relationship between autistic characteristics and TLE, these autistic characteristics were not found to be specific to any epilepsy type, suggesting that autistic characteristics are not related to TLE alone. This is consistent with previous suggestions that behaviours in patients with absence epilepsy, JME, FLE, and tonic-clonic seizures overlap with specific behaviours in those with TLE (Devinsky & Najjar, 1999). However, there was a non-significant trend for more severe autistic-like characteristics during seizure activity in TLE. This is unsurprising given the relationship of autistic traits to the temporo-limbic structure functioning. The findings also support previous suggestions that autistic characteristics may be under-recognised in epilepsy (Steffenburg et al., 2003). Gender was not found to be an indicator for severity of autistic traits which strongly contrasts with previous research (Baron-Cohen et al., 2001). Adults with childhood epilepsy onset did not demonstrate more severe autistic traits, even though childhood epilepsy onset is a factor for autistic characteristics and ASD (eg. Deonna & Roulet-Perez, 2006; Meletti et al., 2003). In Experiment 2, systemizing and empathising abilities were retained, thereby demonstrating that not all abilities were impaired. The findings of intact empathising abilities with seizure activity is inconsistent with evidence that seizure activity disrupts amygdala functioning in those without amygdala damage in TLE, which was represented in the epilepsy sample (Vuilleumier et al., 2004). This research did not find any enhanced relationship between attention-to-detail and systemizing, as attention-to-detail was found to be increased in adults with epilepsy while systemizing was not. However, increased attention-to-detail supported previous evidence of a compulsive attention-to-detail in TLE (Bear & Fedio, 1977). There are no previous studies of systemizing abilities in epilepsy, but these results are inconsistent with previous evidence that enhanced attention-to-detail may be a pre-requisite for systemizing in those with higher autistic traits (Baron-Cohen et al., 2003). However, careful consideration of epilepsy-specific explanations for enhanced attention-to-detail in epilepsy would be warranted, in view of the specific visual deficits associated with epilepsy, specifically TLE. Further, as both systemizing and empathising abilities

remained intact without seizure aura, it is difficult to see how these findings could predict AQ scores, especially as the reverse profile to the autistic profile was demonstrated during seizure activity. Further, these findings are inconsistent with previous research which has demonstrated a deficit of empathising in males and females with ASD (Lai et al., 2011). Note though, these are not core characteristics of ASD. Experiment 4 results indicate that RRBs in adults with epilepsy were not different to the control group, and there was no difference between conditions. However, there was a difference between adults with or without active epilepsy, suggesting that seizure-freedom is related to fewer RRB's. Interestingly, AED control correlated with RRBs in the 'without aura' condition and with social reciprocity during seizure activity in the directions expected, suggesting that AEDs may mask some autistic behaviours. The results from Experiment 4 suggest fewer RRB's may be related to recovery from active epilepsy, which would also be expected given that seizures can be stereotypic events, and repetitive motor actions can be a feature of focal seizures of medial temporal lobe origin (Duncan, 2005). Chronic epilepsy was a factor for severity of social reciprocity with and without seizure activity, demonstrating a progressively negative effect of seizure activity on social reciprocity. However, that recovery from active epilepsy is related to fewer RRBs stands in contrast to the lack of improvements in reciprocal social interactions.

One of the most valuable findings of these initial studies is the strong relationship between AED effectiveness and social reciprocity. This correlation supports previous suggestions that some autistic characteristics may be masked by AEDs (Steffenburg et al., 2003). This is consistent with previous evidence that AEDs reduce socio-emotional impairments (Di Martino & Tuchman, 2001). Chronic epilepsy and poor social reciprocity share a positive relationship. However it is unknown whether chronic epilepsy also correlated with AED effectiveness, and further research would be necessary to explore this relationship. The correlation of RRBs with AED-control for the 'without aura' condition may strengthen the argument that AEDs reduce core characteristics of ASD. No assessment for AED control was conducted in Experiment 1, therefore the relationship between AEDs and autistic traits has yet to be determined. TLE is commonly refractory to AEDs and those with TLE may be at risk from poorly-controlled epilepsy. This may explain the trend for those with TLE towards greater severity of some autistic characteristics in the 'with aura' condition on the AQ.

These studies revealed a number of surprising findings. These findings of higher autistic traits were surprising, given that these traits are considered heritable. In support of this, ASDs are characterised by a deficit in empathising abilities, and intact or enhanced systemizing abilities, which may be heritable (eg. Lawson et al., 2004). The findings of intact empathising are surprising, given that adults with FLE who are specifically impaired in empathising were represented within the sample (Benuzzi

et al., 2004; Farrant et al., 2005). Additionally, intact empathising during epileptic activity is inconsistent with disruption of the amygdala during seizure activity in TLE (Bertram, 2009). The lack of group differences in RRBs are also surprising given that 2 out of 11 items on the SRS-S were from the domain of stereotyped, repetitive behaviours. These items were: Q7: “Compared to others, I have a restricted or unusually narrow range of interests”; and Q9: “I have more difficulty than others do with changes in routine” (Kanne et al., 2009).

Despite the evidence of greater autistic characteristics in epilepsy, autistic traits are considered to be biologically pre-disposed. Generally, despite evidence that autistic traits may relate to an early childhood developmental delay, Experiment 1 suggests that higher autistic traits are found in adults with epilepsy regardless of age at onset. While this indicates that epilepsy may be implicated in autistic traits, it is not known to what extent the adults with epilepsy were pre-disposed to these traits. Experiment 2 may suggest a genuine difference between those with ASDs and adults with epilepsy, as a deficit of empathising was not demonstrated. However, it could equally be argued that empathising abilities are not always found to be deficit in ASD, and have not been found to predict performance on social cognitive tasks (Spek et al., 2010; Dziobek et al., 2008). While the AQ measures 5 domains of autistic traits and provides an overall measure of traits, empathising is only one characteristic of a wide spectrum of deficits. Whether AED control is directly related to empathising abilities has yet to be established, although AEDs are known to reduce socio-emotional deficits (Di Martino & Tuchman, 2001). The poor response rate in Experiment 2 indicated that these tasks may be difficult for adults with epilepsy to undertake. Consequently, these results must be interpreted cautiously and re-tested with a larger sample. Severity of RRBs characterise ASD and predict its severity (Bodfish et al., 2000). In support of such evidence, a strong correlation was found between SRS-S and RRB scores of adults with epilepsy. There was a non-significant trend for higher seizure frequency to be related to an increase of RRBs, but no relationship between RRBs and chronic epilepsy. This may suggest that chronic epilepsy has no long-term impact on RRBs in adulthood onset of epilepsy. Although stereotypy is related to a severe stage of epilepsy, it is not commonly reported as a feature of a seizure aura (Schacter et al., 2008, p.139). Due to its relationship to a severe stage, the ability of participants to self-report stereotypy during a seizure aura may also be impaired. In view of this, the results from Experiment 4 may not reflect the full level of impairment during epileptic activity, especially in consideration of recent findings of a relationship between early-life seizures and impaired behavioural flexibility (Kleen et al., 2011). Further research is needed to clarify the results from Experiment 4. One way to address this would be to assess adults with epilepsy employing the full-scale RBS-R in which Stereotyped Behaviour is constructed as an independent subscale and therefore can be analysed separately. RRB's have been found to be less severe among older individuals with ASD, and given the common pathology, there might be some value in exploring the relationship of chronological age

to RRBs by specifically assessing RRBs in children with epilepsy. These initial findings broadly support previous research, and clearly show that adults with all epilepsy types score higher for specific autistic characteristics, which are negatively influenced by seizure activity. The question remains as to whether these autistic characteristics can recover in those with adulthood-onset of epilepsy after epileptic seizure activity has been resolved.

The aim of Experiments 5a and 5b was to establish whether declarative memory systems were impaired in adults with epilepsy. This would be a crucial factor for impaired performance on the IGT, causing failure to integrate the information needed to track the novel and arbitrary relationships in the task (Guillaume et al., 2009). In addition, the investigation aimed to determine whether the pattern of memory impairment in ASD would be found in the epilepsy sample. This would establish whether the Task Support Hypothesis was a viable model for memory functioning. The TSH proposes that specific relational memory impairments are demonstrated in those with ASD, while memory for single non-relational items remains intact.

Interestingly, a deficit of relational memory was not demonstrated in Experiment 5a. As this was not consistent with the TSH, there is no compelling evidence for the TSH in adults with epilepsy as a viable model. The results of Experiment 5a are inconsistent with evidence of a deficit in relational coding and relational retrieving that is both common and profound in TLE (Drane et al., 2008; Protzner & McAndrews, 2011). This is also inconsistent with evidence that the temporolimbic structures, important for relational memory processing are impaired in TLE, as TLE disrupts semantic networks (Helmstaedter et al., 1997; Troster et al., 1995). Previous evidence has demonstrated that chronic TLE is related to poorer semantic relational processing (Koylu et al., 2006). There was a non-significant trend towards impaired recall for unrelated words, and a non-significant trend towards a relationship between chronic epilepsy and related word recall. An absence of any memory impairment in the epilepsy group contrasts with higher scores on the AQ subscale for poorer imagination. However, the reported use of a memory strategy by participants, lack of clustering, and order of recall, indicate that use of memory strategy may have successfully aided recall. This is plausible given the different kinds of existing evidence including neuroimaging which support this specific deficit in TLE. No instructions were given to participants to avoid using any memory strategy, as contrary to other studies in which this instruction is given, this experiment aimed to replicate the original study in an identical manner. Chronic epilepsy was found to be related to poorer recall of implicit generate words, and there was a non-significant trend towards poorer recall for explicit generate words. The results for Experiment 5b showed that recall in explicit testing and superior completion in implicit testing was intact, with significant improvements for word generation at

encoding. This suggests that declarative memory systems which are crucial for the complex decision making required by the IGT may be intact in adults with epilepsy, which is inconsistent with a number of studies (eg. Leritz, 2006). The adults with epilepsy performed better than expected in Experiment 5b and matched the performance of those with ASD reported by Bowler and his colleagues (Bowler et al., 1997). It would have been difficult for the participants to employ a memory strategy as Experiment 5b presented a large number of stimuli and recall was delayed. Based on recent evidence, effects of lateralisation with the epilepsy sample are unlikely to explain these findings (Protzner & McAndrews, 2011). The epilepsy sample may represent a better functioning sample of the epilepsy population, either through effective use of AEDs, or through self-selection bias as the experiment may have appealed to those with improved memory functioning. Alternatively, there may be a publication bias of memory assessments in pre- or post-operative patients with epilepsy. However, there was value in employing the TSH in light of previous evidence, and the possibility of a potentially useful memory strategy.

Experiment 6 found no significant impairment for identification of facial emotion or rating of facial emotion intensity in adults with epilepsy. The results indicate that FER ability is intact interictally. The amygdala responds to faces and complex social stimuli, contributing to recognising emotion from faces (Adolphs, 2010). As such, the amygdala is implicated in the consequences of experiencing emotional attributes of a situation where somatic states are evoked. Consistent with this, FER is a measure of perception of social cues related to an inability to produce somatic markers (Winston et al., 2003). However, intact FER infers that as the participants correctly identified the facial emotion, they also experienced the emotional attributes of the faces. Therefore, the results suggest that the contribution of the amygdala to somatic marker formation may be intact, and the amygdala should accurately respond to rewarding and punishing stimuli on the IGT task. Despite this, the amygdala is well-known to be extremely susceptible to epileptic kindling and amygdala damage is common in epilepsy. The extent of this damage can be related to impairment of FER (Adolphs, 2001). Such results are inconsistent with previous evidence that the amygdala is implicated in the semiology of TLE, and a feature of several types of epilepsy such as TLE, FLE and IGE (Kullmann, 2011; Farrant et al., 2005; Reynders et al., 2005). Further, chronic TLE negatively impacts upon facial emotion recognition (Meletti et al., 2009). However, in contrast to such evidence, there was a non-significant trend for impaired ability to identify emotion in those with recent onset of epilepsy. Dysfunctional amygdalae are associated with early onset, male gender, and right-sided epilepsy (Golouboff, 2008; Doherty et al., 2003; Salmenperä et al., 2001; McClelland et al., 2006; Hlobil et al., 2008). Early onset epilepsy and male gender were under represented, while right-sided epilepsy was well-represented in the epilepsy sample. Interestingly, impaired FER may be irreversible in adults with early onset epilepsy after surgery (McClelland et al., 2006). However, in support of Experiment 6 results, intact

FER performance has been demonstrated by patients with epilepsy and unilateral amygdala damage (Fowler et al., 2006; Adolphs et al., 1994). Therefore, while the epilepsy sample was small and heterogeneous and no FER impairment was found, this experiment was valuable for evaluating the functioning of the amygdalae and its important role which underpins somatic marker formation.

Experiment 7 provided empirical evidence of significant differences in decision making in adults with epilepsy, leading to the conclusion that somatic marker formation was compromised. Such findings establish that the self-reported social difficulties are genuinely underpinned by cognitive difficulties. The findings reveal an impairment of decision making ability, while there was no indication of hippocampal or amygdala dysfunction. This suggests that the neuroanatomical framework underpinning the SMH did not support a failure to generate markers restricted to either the amygdala or the hippocampus through the specific tasks that were conducted. Given the lack of findings on the TSH and FER, neither appear to be responsible for impaired decision making. The strength of Experiment 7 is that the SMH was established on neurological evidence based on patients with specific anatomical lesions and is a well-established neurological theory. The SMH proposes that damage to the ventromedial sector disrupts the ability to learn due to lack of integration of any emotional component, while other intellectual abilities remain intact (Bechara et al., 1999; Damasio et al., 1996). Crucially, the results from Experiment 7 suggest that the adults with epilepsy demonstrated a lack of ability to learn due to differences in vmPFC functioning. Consistent with this, neuroimaging has associated unilateral hippocampal damage in epilepsy with lower connectivity in the vmPFC (Frings et al., 2009). Lasting alterations in the structure and functioning of the PFC have been related to early-life seizure activity in animal studies (Kleen et al., 2011). The vmPFC has been implicated in selecting and integrating sensory information from the somatosensory cortex. In addition, neuroimaging has implicated the somatosensory cortex in the formation of somatic markers (Lawrence et al., 2009). Consistent with this, somatosensory impairments are common to TLE, and part of seizure semiology (Kasper et al., 2010). Therefore, it can be inferred from Experiment 7 that vmPFC functioning differences are implicated in disrupting the regulation of typical somatic marker formation in adults with epilepsy.

This experiment sought to examine the usefulness of the SMH framework to explain social difficulties in epilepsy. The SMH assumes that an individual can reason about social situations but cannot attach emotional salience to guide their social interactions. Impairments on the IGT by vmPFC patients have been associated with profound difficulties in their social life (Reimann & Bechara, 2010). The results from Experiments 5 - 7 are intriguing, and enable a theoretical understanding in which disrupted neurobiological factors are implicated in a deficit in the typical integration of somatic markers, which

has further implications for social cognitive processing in adults with epilepsy. However, the experiments were unable to establish the contribution of the amygdala and hippocampus to somatic marker formation, thereby providing only a limited explanatory basis of the SMH framework. According to Bechara and Damasio, the contribution of the amygdala and hippocampus to decision making ability may be inseparable (Bechara & Damasio, 2000). Indeed, Yamano and colleagues were unable to establish the contribution of the amygdala and hippocampus in mTLE patients, but they suggest that the right temporo-limbic structures are implicated more than the left structures in decision making (Yamano et al., 2011). Therefore, given the high representation of right-sided epilepsy in the sample, it is not surprising that decision making ability was found to be significantly different in the epilepsy group. However, such findings contrast with evidence that the right amygdala is crucial for FER, which suggests that FER ability would also be impaired in the same group (McClelland et al., 2006; Hlobil et al., 2008). Critically though, Experiments 6 and 7 suggest that a deficit in decision making cannot be a result of any compromised amygdala function as demonstrated by the FER task in this sample of adults. Of note, Dunn and colleagues point out that some vmPFC patients demonstrate impaired performance on the IGT while their emotional reactions measured by their physiological responses are within a normal range (Dunn et al., 2006). The researchers state that the essential theoretical feature of the limbic system framework is that emotion experiences arise from the integration of sensations from external stimuli with bodily information. Therefore, if emotional reactions occur in a typical manner but fail to be integrated in the absence of any deficit in FER, this strongly implicates differences in vmPFC functioning, as the somatic marker signals are regulated within this region.

Ironically, one feature of impaired decision-making but intact FER would be difficulties with understanding ambiguous information in the social world, but with adequate ability to recognise the facial expressions of others responding to any social inadequacies or atypical social behaviours. This suggests that the epilepsy sample group would correctly identify the facial emotion expressions of those around them, but may not understand the emotional reasons behind these expressions. Intact FER ability may therefore result in these adults becoming disconnected from social understandings in their social world, reinforcing a trend towards reliance on a socially-withdrawn lifestyle. The perception of basic facial expressions should trigger affective, motor, and somatosensory experiences which provide meaning from the facial expression. Basic expressions can have different underlying meanings, for example, a smile can imply dominance or enjoyment. According to Chakrabarti, analysis of visual facial features may be sufficient to identify, but be insufficient to integrate identification into a representation of its meaning (Chakrabarti, 2010). This suggests that it may be possible to perceive a smile, but access to the meaning of this facial expression may or may not be

triggered, suggesting that perception of the expression may not always be accompanied by the bodily and neural states associated with the expression.

The question remains whether the bodily and neural states were triggered in the adults with epilepsy so that they experienced embodied states within themselves during their perception during the FER task. However, there is some doubt as to whether these triggers genuinely occurred, as eight participants with epilepsy reported that they found the FER task difficult and stated that they had not performed well. This would be consistent with higher scores in the initial studies of self-reported abilities in the AQ (Q.36): “I find it easy to work out what someone is thinking or feeling just by looking at their face” and the SRS-S (Q.6): “I have trouble understanding the meaning of other people's tone of voice and facial expressions”. As such, there may be some incongruity between identifying facial emotions and experiencing embodied states which contribute towards a deeper understanding of the meaning of the facial expressions. This would be consistent with failure to experience the neural states of the facial emotion, while still demonstrating the ability to recognise facial emotions. One explanation for intact FER may be the use of a strategy based on previously learned identification skills for adults with adulthood onset of epilepsy. The use of such a strategy would be consistent with findings of impaired decision making abilities resulting from impaired somatic marker formation, and intact FER ability. Deficits of FER in adults with TLE are hypothesised to be related to disruption of a critical period of life for establishing the neural network underlying FER, and may be a developmental disorder in early-onset TLE (Meletti et al., 2009; Bonora et al., 2011). However, there was some value in employing the FER task in light of this possibility, not least because age at first seizure (febrile) and age at epilepsy onset may differ. Additionally, recent evidence suggests there may be existence of a common neuro-developmental phenotype for TLE (Voets et al., 2011). It is unknown whether pre-existing autistic traits were the results of developmental factors which presented before the onset of epilepsy, and there has been some suggestion of some autistic-like difficulties preceding seizures in childhood epilepsy. However, the influence of declarative memory on decision making abilities cannot be underestimated, and while Experiment 5a failed to find the specific memory patterns demonstrated by those with ASD, the epilepsy group performed better than the existing literature suggests. The trend for poorer recall of related words to chronic epilepsy suggests that there may be a weakening of semantic relatedness relative to epilepsy duration. However, to date there is a gap in the research related as to whether developmental factors influence this trend. Interestingly, and contrary to the current literature which suggests that memory difficulties are the most common difficulty in epilepsy, it could be inferred that decision making ability may be more severely impaired than memory recall. One explanation may be that the adults with epilepsy employed a compensatory strategy for memory difficulties, but were unable to use a strategy for decision making under ambiguity. Differences in somatic marker

formation hinders how new information is integrated into existing information, affecting the speed of social learning. In the social environment, social interaction can be continually changing, leading to difficulties in keeping track of social complexities. This may be especially so where there are multiple social interactions are occurring at the same time. The SMH can provide a theoretical explanation for a generalised deficit in social cognition, which would be consistent with the poorer social skills and poorer social reciprocal interaction demonstrated in the initial studies. Similarly, such findings are consistent with the social difficulties reported by adults with epilepsy (McCagh et al., 2009). Such evidence demonstrates that given the higher autistic traits and characteristics, social cognitive impairments may have previously been under-recognised in adults with epilepsy. In the IGT tasks, the decks are constantly either advantageous or disadvantageous throughout the task. The real social world is not always so constant. If contingencies were to be constantly changing however, this would have immediate consequences for the adults with epilepsy, who demonstrated difficulties with somatic marker formation and integration occurring early in the task. Initial delays in somatic marker formation would mean that adults with epilepsy have little guidance throughout their social interactions. Conversely, were contingencies to remain constant and repeated over a longer time period, the lack of any significant difficulties in the final block of the IGT task suggests that there is a benefit for persevering with the task. The fast improvement in somatic marker formation at the end of the IGT task suggests that a quick and strong gut feeling occurs sometime later after the initial delay in adults with epilepsy. This pattern suggests that perseverance and repetition with the same contingencies may provide further guidance, and may deliver a social reward. This sudden late shift in somatic marker formation may present itself as a strong gut feeling, after which the individual may have increased social understanding, and subsequently be driven towards a sudden behavioural change.

Frequent seizures in childhood may lead to irreversible connectivity changes in important neuronal pathways (Kellinghaus et al., 2004). Importantly, early-life seizure activity has been related to unrecoverable damage to the structure and functioning of the PFC and inflexible behaviour (Kleen et al., 2011). However, there is a paucity of evidence for what abilities are recoverable for adulthood-onset of epilepsy. In addition, cognitive inflexibility has not been well-researched in these adults. While poorer attention-switching in the epilepsy group provided a measure of cognitive inflexibility, this difficulty was not reflected in higher levels of sameness behaviours compared to the control group. While this is surprising, the epilepsy adults without ‘active epilepsy’ reported fewer RRB’s suggesting that some improvements are related to seizure-freedom. This contrasts with an absence of improvements to poorer social reciprocity through seizure-freedom. However, there may be different timelines for recovery of these abilities. Throughout the research, findings from the ‘without aura’ conditions show strong evidence of impaired social functioning measured in social skills, social

reciprocity, and decision-making abilities, while RRBs, memory and empathising abilities remained intact. Consistent with this, seizure activity was found to negatively impact upon social functioning again, measured by differences in social skills and social reciprocity, but not RRBs or empathising. This implicates seizure activity with the negative effects on very specific cognitive processes that are important for social functioning. Difficulties in social skills and reciprocal social behaviour can be explained by differences in the neural basis of social cognition, provided by the somatic marker hypothesis. This may account for difficulties regulating social interaction, exhibiting appropriate social behaviour, developing appropriate social relationships and understanding the conventions of social interaction.

Generally, the main findings in Experiments 5-7 are consistent with the initial experiments. The defining characteristic of ASD is a deficit in social cognitive functioning, and it was empirically established in this research that social difficulties were associated with significant differences in somatic marker formation in adults with epilepsy. These research findings suggest that neurobiological systems may operate differently for those with epilepsy by influencing social cognitive processes. This neurobiological perspective fits well with the epilepsy group, especially given that epilepsy is a neurobiological disorder.

10.3 Factors for autistic characteristics

The evidence suggests that having epilepsy increased the risk of some autistic characteristics. Adults with epilepsy had increased autistic traits, poorer social responsivity, and poorer decision making abilities due to difficulties with the formation of somatic markers. Recovery from epilepsy was related to fewer restricted and repetitive behaviours, but was not associated with improved social responsivity. However, it is presently unknown whether individuals in the ex-epilepsy group in this research project are pre-morbidly pre-disposed to be more likely to recover from epilepsy. The evidence also suggests that epileptic activity itself may increase the risk of autistic characteristics, as some characteristics were found to be negatively influenced during seizure activity which were measured by the AQ and SRS-S. The effects of seizure activity therefore has implications for autistic characteristics. The reason why this is so important is that despite evidence that seizure auras can last only minutes, recovery from epileptic activity can last up to 48 hours (Fisher & Engel, 2010). According to Fisher and Engel, the cognitive, emotional, and behavioural disturbances persist throughout this time (ibid.). The direct relationship between seizure activity and somatic marker formation is currently unknown; however ictal epileptic discharge propagation to the medial frontal brain regions is found in patients with focal epilepsy and this may additionally implicate IEDs as a factor for disruption to somatic marker formation (Laufs et al., 2007). Many adults report daily

seizure activity, and it is important to recognise that the post-ictal stage of epilepsy may also have implications for the durability of these characteristics. To this end, it is fair to say that seizure auras are not momentary autistic-like characteristics, but a small part in a sequence of changes beginning even before the seizure onset.

Of course, like every epileptic seizure, seizure auras can be potentially dangerous resulting in brain damage by inducing neuronal death, therefore active epileptic activity has lasting implications for the development of autistic characteristics in the mature adult brain. Consistent with this, chronic epilepsy was associated with decreased social responsiveness, both with and without epileptic activity. Chronic epilepsy was a factor for severity of autistic characteristics, and was associated with decreased social responsivity in Experiment 3. This may infer a direct relationship between continual seizure activity and these characteristics. Further research on the relationship between chronic epilepsy and social and non-social autistic characteristics would be valuable. However, frequency of seizures did not affect the severity of these autistic characteristics. Further, the lack of a frequency effect on autistic characteristics suggests they may be associated with having epilepsy, rather than the amount of seizure activity. Alternatively, it may also be suggested that it is the combined presence of IEDs and seizure activity that are related to autistic characteristics, as a high frequency of IEDs is found in both epilepsy and ASD. Age at onset of epilepsy was only assessed in Experiment 1, and no relationship was found between childhood-onset and autistic traits. This was surprising, given that childhood-onset of epilepsy is related to more severe amygdala damage, and as such, poorer socio-emotional functioning. However, TL seizure discharges have specific involvement in activating the amygdala at all ages, which may explain the lack of significant differences between childhood or adulthood epilepsy onset. No effect was found for gender on measures of autistic traits employing the AQ. This is surprising given the existing high-co-morbidity, and the wealth of evidence of gender differences in those with ASD and in the general population. One consideration may be whether AEDs compensate for severity of autistic characteristics differently for males and females, as consideration of gender is an established practice in the choice of AEDs in epilepsy (Bauer et al., 2011). The lack of findings, although inconsistent with the typical gender patterns found in measures of the AQ, are consistent with evidence that no major gender differences for cognition and behaviour have been found in epilepsy (Baker, Aldenkamp, & Meador, 2004). Supporting this, is evidence that suggests epilepsy has no sex boundaries, affecting males and females equally. Taken together, this would be consistent with the view that these characteristics are ‘epileptic’ rather than ‘autistic’ in their genesis. Interestingly, this increases the need for further research of gender and autistic traits in epilepsy.

AEDs improve 2 core features of autism: communication and socialisation (Di Martino & Tuchman, 2001). In their review of AED use in ASD, Di Martino and Tuchman highlight that autism, epilepsy, and affective disorders may share commonalities as the same neurotransmitter systems are targeted by AEDs. Interestingly, improvements in behavioural and communication skills in ASD correlate with the control of epilepsy or epileptic discharges. While Di Martino and Tuchman found that improvements of core features occurred regardless of seizure control in ASD, evidence in this research project suggests that self-rated effective seizure control was related to improvements in social reciprocity. It was also found to be related to improved restricted and repetitive behaviours. Together, this provides evidence which suggests that AED control is related to severity of autistic characteristics, indicating that adults with poorly controlled chronic epilepsy may have more severe autistic characteristics. This is consistent with previous research that AEDs can reduce some of these characteristics, and suggests that the spectrum of autistic characteristics is likely to be most severe in adults with untreated or uncontrolled epilepsy. As AED control was self-rated, further empirical research is needed to establish a relationship between AEDs and autistic characteristics. However, the findings of this research together with the existing literature on AEDs suggest that untreated adults will have a more severe presentation of autistic characteristics, and adults with ineffective AEDs will also have more severe autistic characteristics than those with effective AEDs. Research of autistic traits in untreated adults with epilepsy is lacking, but again, this would be a useful investigation. Indeed, it could be strongly argued that the true extent of autistic characteristics has not been fully identified in this research, due to lack of participants with epilepsy not taking AEDs. AEDs are commonly refractory in TLE and known to improve socio-emotional functioning, therefore if social cognitive difficulties are common to all epilepsy types, lack of masking of socio-emotional difficulties in TLE would strengthen the argument that an epilepsy personality type exists, but is only revealed in those who are untreated or uncontrolled by AEDs. Chronic drug resistant TLE has been related impairment of FER, which raises the question about whether successful AED intervention may also mask other non-core autistic characteristics in epilepsy. What could not be determined was whether AED correlations reflected overall improvements as a result of other undetermined factors. The genuine extent of the presence of autistic traits and characteristics in epilepsy before pharmaceutical intervention is presently unknown and first and foremost, research should aim to establish the extent of this relationship.

Factors for the spectrum of autistic characteristics

A number of factors that increase autistic characteristics were identified. As previously discussed, chronic epilepsy negatively correlated with autistic characteristics both with and without seizure activity. This reveals a cumulative risk for increasing autistic characteristics increasing with chronological age. This evidence should be considered alongside the cumulative effects of epilepsy

in ASD, which increases with chronological age. Together these findings demonstrate an inverse relationship in the co-morbidity, suggesting that each condition, if uncontrolled or unresolved, is predictive of the other. The second strong factor is AEDs. Effective AED control correlated with improvements in social responsiveness and RRBs, supporting previous evidence that AEDs mask autistic characteristics. In addition, clear relationships were found between autistic characteristics and seizure activity. This is consistent with existing evidence of disruption of functioning by seizure activity on the MTL, which has been strongly related to autistic characteristics. Several factors that were expected were not found. No gender differences were identified for autistic traits. No differences were found between childhood and adulthood-onset of epilepsy, and no major differences were found for specific epilepsy type. The real strength of these experiments is that they represent a systematic study of autistic characteristics in epilepsy, and the large sample sizes achieve good statistical power. Other experiments were limited by their smaller sample size, and lack of male participants. This is important, as ASD is associated with a higher male ratio. Consistent with previous research, these experiments suggest that social difficulties in adults with epilepsy may be under-recognised.

The pattern of autistic characteristics defined in this research project are subject to patterns of propagation of epileptic activity upon the brain, dependent not only on the contribution of underlying structures and location of seizure onset in the brain, but on the functional networks disrupted during seizures and how these networks interact with each other (Bettus et al., 2011; Grant, 2005; Epilepsy Research UK, 2011). These networks can vary according to epilepsy type. However, adults with epilepsy may have several epilepsy types, and seizure auras are found in several epilepsy types in addition to TLE. As such, autistic characteristics will differ in severity according to the functional networks implicated in the primary epilepsy type, but may be common to most adults with epilepsy.

Despite the high co-morbidity of ASD in epilepsy, RRBs were not found to be significantly increased in the epilepsy group. However, according to Happé and colleagues, RRBs are not good markers of autism in infancy, and their large population based study revealed low-to-moderate correlations between autistic-like behavioural traits suggesting that the 3 core characteristics are relatively independent of each other (Happé et al., 2006). Interestingly, the ex-epilepsy group reported significantly less repetitive behaviours compared to those with active seizures. There was also significant reduction of these behaviours with good AED control of seizures. Further research is needed to establish whether RRBs may be a feature of uncontrolled and untreated epilepsy. On the same note, this research should establish whether taking AEDs when seizures have resolved contribute towards fewer RRBs in the ex-epilepsy group. Taking AED into account, if a relationship between RRBs were found to be an indicator of having active epilepsy, this might suggest homogeneity in all 3 core characteristics.

Further research is needed to establish why adults who no longer have seizures report improvements in RRBs. Even though some ASD characteristics such as decreased empathising and enhanced systemizing abilities have not been demonstrated in this project, there is variability in the autistic characteristics in adults with epilepsy that is comparable to existing research of adults within the autism spectrum, despite the AED intervention.

10.4 Inferences

The findings of increased autistic traits in a heterogeneous clinical sample questions the extent to which these traits are attributable to heritable characteristics of ASD or attributable to a non-heritable acquired diagnosis of epilepsy. This research demonstrated that the increased autistic traits were not related to having childhood-onset of epilepsy, or to any known developmental dysfunction, and no gender differences were found. A valuable future line of enquiry would be whether gender differences for autistic traits can be found in a group of adults with unresolved early childhood-onset of epilepsy. This would raise questions about whether young males, who are especially vulnerable to a more severe presentation of epilepsy, would be vulnerable to a more severe presentation of autistic characteristics. There is already research evidence indicating that males are more prone to severe brain abnormalities from seizure activity, resulting in more brain damage in males (Briellmann et al., 2000). On the one hand, higher autistic traits suggests that these traits are related to having epilepsy. As epilepsy is largely non-heritable and can be acquired, relatives of adults with epilepsy are unlikely to have increased autistic traits. On the other hand, autistic traits are heritable even in the general population suggesting that relatives of adults with epilepsy may have higher autistic traits than relatives of adults without epilepsy. Further research is needed to establish whether these autistic traits are heritable, or whether they are a consequence of acquiring epilepsy even at the very early stages of life. Until further research has established the extent of an autistic phenotype in epilepsy, no further conclusions can be made from these findings.

Inconsistent with some previous evidence, poor social responsiveness was demonstrated in the ex-epilepsy group. This may be due to a sample bias, with the ex-epilepsy group representing a group of adults recently seizure-free rather than long-term seizure-free, as it could be argued that long-term seizure-free adults may be less motivated to participate in epilepsy research as they no longer have seizures. Replication of Experiment 3 could include adults who have been seizure-free for many years, and analysis could be conducted to investigate whether social reciprocal abilities are related to the length of time since their last seizure. It has yet to be established whether adults with all epilepsy types have social cognitive difficulties. Previously, research has shown that early-onset epilepsy is associated with more impaired performance on ToM and FER tasks. This could imply that while

adults with adulthood-onset epilepsy have difficulties with social cognition, childhood-onset may be a factor for severity of social cognitive difficulties. This would be consistent with findings from Experiment 3 which demonstrated that adults have impaired social responsiveness but that chronic epilepsy is a factor for these difficulties.

The close relationship between early epilepsy onset and children with ASD with a learning disability was demonstrated by Steffenburg (2003). By comparison, this research project has demonstrated a relationship in adults between active epilepsy and autistic characteristics without a learning disability. As early onset of epilepsy is related to learning difficulties, there appears to be a direct relationship between active epilepsy and autistic characteristics, with or without learning disabilities. Overall, the experiments in this research project provide evidence of a spectrum of some autistic characteristics within a heterogeneous group of adults with epilepsy, in which the presence of social difficulties may be related to an impairment of social cognitive functioning, which is under-recognised.

10.5 Considerations

This section sets out to address further epilepsy-specific considerations that were not addressed in this research project.

Resolution of epileptic seizures

At present, there is no evidence that resolution of epilepsy leads to improvements in the autistic characteristic of social responsiveness, therefore it could be argued that resolution of epilepsy is not always congruent with improvements in cognition and behaviour. However, it takes many years to recover from the damage of epilepsy, and recovery time depends on how chronic the epilepsy was before resolution. Further, AEDs can mask the true recovery pattern, since many adults with epilepsy continue to take AEDs after cessation of seizures. There is a lack of research investigation and a lack of understanding of the recovery pattern from autistic characteristics in adults and children with epilepsy. Such knowledge would be valuable, especially for early epilepsy onset in newborn infants. If psychology researchers could identify the pattern of recovery, then it could be established whether those with epilepsy completely recover from autistic characteristics, and what factors determine the length of this recovery. If adults with epilepsy have cessation of autistic characteristics where epilepsy is resolved, this could establish these characteristics are truly acquired, are dependent on the presence of epileptic activity having occurred, and have the potential for some adults to be subsequently resolved.

Autistic Behaviours as a defensive avoidance strategy against limbic seizures

This section will now discuss whether autistic behaviours are defensive against the onset of multiple IEDs leading to seizures during IED activity. There are multiple factors that may influence these research findings; however the impact of IEDs must be taken into consideration. One consideration that the research did not address was the role of epileptiform discharges within the limbic system, and whether interictal epileptiform discharges influence social interaction. The presence of IEDs is a remarkable feature within the co-morbidity. These IEDs are not simply benign; indeed, the hypothesis that IEDs exert a deleterious effect on behaviour and cognition is supported by their abnormally high prevalence in children with developmental disorders (Van Bogaert et al., 2012). Fisher and Engel (2010) suggest that epileptiform EEG events during the interictal state are really fragments of seizures (Fisher & Engel, 2010). Edward Bertram (2009) provides an explanation, discussed in detail in Chapter 2, on why IEDs at the seizure foci do not always transgress into a seizure. The distribution of IEDs across multiple sites at seizure onset play a particular role in the evolution of a seizure, and as IEDs are related to changes in behaviour and cognition, this suggests that IEDs may also be crucial to understanding why adults with epilepsy behave in the way that they do.

Bertram hypothesised that there are multiple independent generators of seizures creating seizure onset in limbic epilepsy, implying that each site can initiate a seizure independently, or drive another site into a seizure, one seizure can be driven by the amygdala and another by the hippocampus. Given that not all epileptiform discharges result in seizure activity, the primary motivation of the adults with epilepsy of limbic origin should be to ensure epileptiform discharges remain interictal. If Bertram's hypothesis is assumed, avoiding activation of one of the multiple seizure generators such as the amygdala or hippocampus under specific conditions may provide a useful defensive strategy against seizure onset. If the hippocampus is driving the amygdala to initiate onset, its success may depend on existing activation levels of the amygdala. Therefore avoidance of environmental triggers or stressors that result in arousal of specific limbic sites may prevent multiple site activation that would normally result in interictal epileptiform discharges independently initiating a seizure. The success of seizure reduction may depend on whether the individual can recognise or has knowledge of what factors contribute to activating the specific remote site. It is well recognised that individuals with epilepsy have reported that certain triggers within the environment make a seizure more likely. According to Spector and colleagues (2000), 52% of adults with epilepsy consciously try to avoid seizure precipitants. For the individual to successfully prevent a seizure, time may be needed to employ a defensive strategy. Recent research has identified significant changes in neuronal activation in areas remote to the focal seizure onset minutes before the seizure actually begins (Truccolo et al., 2011). This is consistent with Bertram's description of how seizures start with an assemblage of neurons across a circuit, in which the interactions determine if a seizure will occur. Finally, there would need

to be evidence of a seizure attempting to start correlating with behavioural changes. The implications for behavioural change at this crucial time point is the significant advantage for those with epilepsy to avoid triggers which would stimulate activation of the amygdala or hippocampus to drive the seizure during epilepsy kindling. For example, these behaviours might include eye-gaze avoidance, since eye-gaze increases intimacy and stimulates amygdala activation in the observer (eg. Chakrabarti, 2010, p.440). Further, given that language may stimulate activation of the hippocampus, avoiding use of language may reduce stimulation of another critical site in which it is relatively easy to elicit seizures. From this perspective, unusual social behaviours such as social responsivity, communication, and eye-gaze may provide an epilepsy-specific advantage by minimising the likelihood of one limbic region to drive a remote region into seizure activity by reducing activation in the remote site. These unusual and specific behaviours might be interpreted as autistic characteristics in adults with epilepsy. Such avoidance or ‘defensive’ behaviours would be consistent with the assumptions that seizures arise from the interaction of the environment, and that mental states, emotional states and sensory input can trigger seizures (Spector et al., 2000).

There are multiple theoretical models explaining factors which increase the likelihood of a seizure being triggered, such as the impact of stress and cortisol (Eggers, 2007). However Bertram’s explanation is based on the epileptogenous of seizure activity and its’ explanation is embedded in the seizure threshold levels required across multiple sites to induce seizure activity. This would be consistent with the presence of epileptiform discharges having an association with atypical behaviours and cognitive functioning (Capdevila et al., 2008; Binnie & Marston, 1992). This would be consistent with evidence showing a relationship between IEDs and severity of ASD demonstrated by Muñoz-Yunta and colleagues (2008), and also a correlation between IEDs and symptoms of ASDs by Yasuhara (2010). Taken together, both these studies are consistent with findings in this research project, as more epileptiform discharges occur during a seizure aura than without. Given these findings, Bertram’s hypothesis provides one explanation for this relationship. It provides an alternative explanation to underconnectivity as a hypothesis for lack of epileptic seizures in those with ASD (Hughes, 2007). Adopting defensive behaviours would be consistent with the perspective that individuals with epilepsy have a spectrum of self-control behaviours in stressful situations, either to avoid seizure precipitants or to terminate seizures (Spector et al., 2001). However, it has yet to be determined whether perceived self-control of seizures are related to unusual and specific behavioural patterns which are identifiable as autistic characteristics.

Protective strategies, adverse effects of cortisol

This section will now discuss whether autistic behaviours are protective against stress which may lead to the onset of IEDs, which can cause changes in cognition and behaviour (Fisher & Engel, 2010).

Research investigating stress in children with and without ASD during an ecologically valid benign social interaction found that those with ASD had significantly higher cortisol levels, reflecting enhanced arousal from social engagement (Corbett et al., 2010). This study demonstrated that not just stressful social interaction but ‘benign’ social interaction results in the increase of cortisol in those with ASD. This is important as according to Eggers, TLE is distinct from other epilepsies as the seizures are provoked, usually by stress (Eggers, 2007). According to Eggers, cortisol rises increase the risk for seizure onset. These studies illustrate that increases in cortisol levels due to social stress may have negative consequences in those with ASD and TLE. In individuals with TLE, there may be an epilepsy-specific advantage for avoiding social interaction for those with seizures, which may result in arousal from social engagement. Importantly, social interaction itself may be harmful to those with autistic characteristics who have limbic seizure activity. Children and adults with ASDs often find social interaction stressful and underlying seizure activity, where detected, may provide one explanation why this might occur. Clearly, as high cortisol levels could have a detrimental effect on seizure activity, social interaction itself may have lasting negative effects during the critical onset stage of epilepsy. It remains to be determined whether social interaction can increase the likelihood of seizure activity specifically in TLE.

Genesis of epilepsy

These experiments have highlighted that a lack of any ASD diagnosis and late presentation of epilepsy in adulthood is consistent with autistic characteristics relating to the genesis of epilepsy rather than autism. Evidence for this could be provided by adults who no longer have active epilepsy, and have reduced autistic characteristics. However, Experiment 3 showed that social responsiveness did not recover where epileptic seizures were resolved. This is important, and further research is required to re-test these findings and establish why recovery for social functioning is poor.

Understanding Autistic Behaviours in Epilepsy

This research project has explored several factors implicated in the presence of autistic behaviours in epilepsy. The following table summarises their relationship to stages of epilepsy, however AEDs are not included as a factor in this table as some adults with epilepsy are uncontrolled or untreated.

Table 10.2: *Relationship of Behavioural Spectrum to Epilepsy*

Genesis of Epilepsy	Ictal stage of Epilepsy	Interictal stage * of Epilepsy [with IEDs]	Chronic Epilepsy	Resolution of Epilepsy
Permanent behaviours: Occurring while epilepsy is active, related to age at onset, eg. language	Variable behaviours: Related to seizure aura stage, eg. stereotypic behaviours, social interaction	Variable behaviours: Related to, for example, environmental cognitive and sensory demands: i) protective strategies, eg. avoid sensory stimuli related to cortisol increases in TLE ii) defensive strategies, during IED activity eg. social interaction avoidance	Accumulative behaviours: Severity of behaviours related to length of active epilepsy	Resolving behaviours: When epilepsy is inactive. Related to: i) age at onset; ii) length/severity of epilepsy and epilepsy-related damage; iii) time since last seizure

* Note that IED activity is not benign (eg. Fisher & Engel, 2010)

10.6 Wider implications

To my knowledge, this is the first systematic and comprehensive investigation of autistic characteristics in adults with epilepsy. The first major finding is that adults with epilepsy without a diagnosis of ASD reveal higher autistic characteristics compared to a control group, and these characteristics increase and decrease with seizure activity. These results indicate a relationship between epileptic activity and autistic characteristics. However, there are difficulties in establishing that all autistic characteristics are strongly associated with active epilepsy. Repetitive behaviours and FER ability were not found to be significantly related to having epilepsy or to seizure activity. The strengths of the initial research are that some experiments were conducted on a large sample and have good statistical power of analysis, such as the SRS-S. Other experiments are limited by their small sample, and therefore have low statistical power. The second major finding is that compromised somatic marker formation may explain social difficulties in adults with epilepsy. The strength of the main experiments is that the epilepsy group were naïve to the decision making experiment as an empirical measure of social cognitive ability, and that the SMH is well established with regard to neural networks implicated in the processes, across many clinical groups. The extent to which patients present autistic characteristics before their diagnosis is unknown. It would be valuable to establish this, as initial characteristics would be congruent with a pattern of co-morbidity in ASD. The literature review of research in ASD adults revealed a remarkable lack of consideration to the co-morbid diagnosis of epilepsy. Given that TLE disrupts semantic networks and is related to FER impairments, this would be a worthwhile consideration for future research, especially as this thesis presents new evidence of a general social cognitive dysfunction.

ILAE Recommendation

This research project does not directly provide supporting evidence for the ILAE recommendation to eliminate the distinction between the different types of focal seizures such as complex partial and simple partial seizures (Berg et al., 2010, p.678). However, this research project is consistent with existing evidence that epileptic activity in focal epilepsy may cause widespread disruption and alteration across networks which challenges the concept of ‘focal epilepsies’ (see 2.7). Further, it challenges the concept of ‘generalised’ epilepsy being historically distinct from focal epilepsy, as no distinction was found between epilepsy types in Experiment 1 during the interictal stage. This supports the outcome of previous studies which continue to challenge current classifications of epilepsy, and potentially provides a basis for further revision.

Therapeutic intervention

The research findings suggest that there could be benefits for therapeutic intervention to acquire a specific focus on autistic characteristics. Such intervention could help family and carers of adults with epilepsy recognise and address these characteristics. A re-evaluation of the way that adults with epilepsy receive psychological intervention, as well as the way in which they interact with those who manage their epilepsy is required, as this research has provided evidence that social interactions may be hindered. According to Jokeit, identifying deficits in social cognition in adults with epilepsy would allow for the development of more specific treatment strategies aimed at improving social-cognitive abilities (Jokeit, 2010). Further, social cognitive ability is not always part of the psychiatric or neuropsychological assessment of epilepsy patients (ibid.). However, given the high presence of autistic characteristics, this assessment is vital. The recognition and identification of deficits in social cognitive abilities should lead to the development of specific treatment strategies for improving social cognitive abilities as an integral feature of epilepsy management. This research has implications for neurologists, primary care managers, epilepsy nurses, epilepsy help-line advisors, surgical consultants, Epileptologists, and those who provide information on AEDs to adults with epilepsy.

10.7 Future Research

Replication

Future research replicating the experiments in this research project would be valuable to improve the strength of the conclusions of this thesis. It would be worthwhile investigating social responsiveness with the 65-item full scale assessment in adults with epilepsy. Likewise, it would be worthwhile investigating restricted and repetitive behaviours with the 43-item full scale assessment in adults with epilepsy. An additional investigation of autistic traits of untreated and uncontrolled adults with TLE could be valuable. Replication of empathising abilities would benefit from conducting analysis to

explore the effects of AEDs. Likewise, replication of the IOWA task performance and the effects of AEDs would also be valuable.

Investigative

Given the findings from Experiment 1, a valuable line of enquiry would be to establish whether these autistic traits are heritable. Such research should investigate why the AQ was unable to distinguish those adults with childhood and adulthood-onset epilepsy. The effectiveness of AED control and severity of autistic characteristics should also be examined. A comparison between adults with epilepsy with and without AED intervention could be rewarding, and provide a genuine measure of characteristics before being potentially masked by AEDs. The presence of IED's and their role in cognitive and behavioural changes is intriguing, and very little research has provided insight on their relationship to autistic characteristics. Future research should focus on addressing the relationship of IEDs to avoidance behaviours, specifically social and sensory avoidance, as this may be an additional unrecognised factor for the spectrum of autistic characteristics within the epilepsy group. A further interesting line of enquiry would be to investigate whether autistic characteristics in childhood is a predictive factor for identifying those who may have a neuro-developmental cause for the onset of TLE in later adulthood. The investigation of a neuro-developmental cause may be valuable for early intervention in childhood. Such research should investigate autistic traits in the relatives of those with neuro-developmental epilepsy. It may also be valuable to investigate whether there are predictive factors in childhood such as higher rates of stereotypy which can identify those with ASD who develop epilepsy in later adulthood. Fisher and Engel (2010) suggest that epileptiform EEG events during the interictal state are really fragments of seizures (Fisher & Engel, 2010). Therefore, future research could explore the relationship of interictal epileptiform discharges directly to autistic characteristics in adults with epilepsy, as this research project did not measure the presence or frequency of these discharges. This research would support previous findings of a correlation between IEDs and ASD symptoms in ASD, and could provide valuable empirical evidence for the determining whether there is a causal role of IEDs for autistic characteristics regardless of any pre-existing diagnosis (Yasuhara, 2010).

Development of Treatment Program

Future research could focus on helping adults with epilepsy to identify and reach their own social goals in view of findings in this research project.

Limitations

This research was limited by the adults with epilepsy who were not strongly represented in these experiments which included males, recent-onset adults, adults with neuro-developmental epilepsy, and those not taking AEDs. The participant sample in Experiments 5-7 represented a heterogeneous group of adults with epilepsy who were predominantly female, with right-sided epilepsy. It could be

inferred that the individuals who travelled to the University of Bath to participate in this research may represent a group of higher-functioning adults with epilepsy. Further, these adults were recruited from Epilepsy conferences and UK universities and were therefore active in the community, suggesting that they may represent a more socially active group of adults with epilepsy. The selection process excluded adults with ASD; however it did not seek to exclude adults with epilepsy who had any psychiatric illness such as depression or anxiety, head injury, hypoxia, or a personality disorder which may have influenced the findings from Experiments 5-7. The presence of other neurological conditions were investigated and noted in Table 8.3. As such the findings from this small sample may not be representative of all adults with epilepsy in the general population due to sample selection bias.

Experiments 2,5,6 and 7 were limited by sample size which resulted in low power in the analysis, and multiple regression analysis or subgroup analysis could not be conducted. Experiment 2 had a poor response rate, suggesting that these tasks were not easy to undertake. One way to address this would be to send Experiments 2a and 2b out separately. Experiment 3 lacked participants that completed both conditions, however it benefitted from a larger sample size. Experiment 1 was limited by lack of data on AED control, and given the later correlations it may be that AEDs significantly affected the results of this experiment. However, this was addressed in Experiment 3. In addition, the AQ consisted of statements about childhood, which were not appropriate for adulthood-onset epilepsy participants. One way to address this would be to exclude the AQ childhood statements and perform analysis between adulthood and childhood-onset on the remaining data.

The new epilepsy-specific method was successful in providing specific self-reported information about seizure activity and may be valuable for resolving some previous difficulties with validity (Besag, 2004; Krishnamoorthy, 2006). Assessing the seizure aura stage of epilepsy provided valuable information, but these scores should not be over-interpreted for this condition as this stage is only applicable to approximately half of the individuals with epilepsy. It is unknown whether self-reporting for seizure auras related to epileptic seizure activity or subclinical seizure activity, however as the reporting is reliable and adults with epilepsy have been demonstrated to under-report especially for mild seizure activity, the results suggest that the findings are more likely to relate to epileptic seizure activity.

The findings from a methodological perspective appear to indicate that measuring the seizure aura stage may be easier and more useful for some assessments and tasks than others. Additionally, the implications of the findings from a methodological perspective appear to indicate that seizure activity in adults with epilepsy may influence the severity of autistic characteristics or any pre-existing autistic

traits, and is consistent with findings that the presence of epilepsy increases the severity of autistic characteristics in those with ASD. However, a family history of autistic traits or autism spectrum disorders was not sought in any experiment from either the epilepsy or the control groups, which limit these findings. The literature review did not find any experimental psychological studies which had accounted for the influence of epileptic activity as a factor for performance during tests to establish autistic characteristics. Given that epilepsy is not a static condition and that epileptiform discharges can be sporadic, it is unsurprising that experimental results in these studies were sometimes contradictory. In view of this, the presence of epilepsy may be able to account for some variability of autistic characteristics, and should be a consideration in future research. Further, even though there is an underlying assumption that epileptic seizures have a more negative impact than epileptiform discharges, Engel and Fisher state that IEDs may actually be seizure activity (2010). Whether persistent and frequent epileptiform discharges can result in autistic characteristics without epileptic seizures has yet to be determined.

The enquiry into AEDs in this research was essentially based on the relationship of AEDs to autistic characteristics, either single or multiple. Therefore, participants were not required to rate whether they were receiving monotherapy or polytherapy, as this was not the aim of this research. However one AED, valproic acid, can impair complex decision making (Cavanna, 2010).

In Experiment 4, care needs to be taken when interpreting stereotypic behaviours in the seizure aura condition due to the close relationship of epilepsy and stereotypic behaviours. This is because adults with epilepsy may be unaware of their own stereotypic behaviours following their seizure aura, but they may be aware of their day-to-day repetitive behaviours. In view of this, stereotypy needs to be separated as a subscale, to improve the strength of the conclusion of the relationship between RRBs and active epilepsy. In Experiments 3 & 4, the analysis between adults with or without active epilepsy generated two mutually exclusive dichotomous groups. This limited the possibility of analysis between performance and years of seizure freedom, which may have improved the strength of the conclusion from these experiments.

Finally, as EEG was not conducted in this research, one factor not controlled for which may influence the variability of the spectrum of autistic characteristics in adults with epilepsy may be IEDs. These discharges repeatedly disrupt hippocampal and amygdala functioning where there is onset of seizure activity of limbic origin (Bertram, 2009).

10.8 Summary

This research set out to explore autistic characteristics in relation to epileptic activity, and has succeeded in this aim by identifying the extent of these characteristics. This research demonstrated for the first time the effect of mild epileptic activity on the cognitive and behavioural characteristics of ASD, in a manner which was epilepsy-specific. The initial experiments identified the extent of autistic characteristics and factors influencing their severity. Importantly, the main experiments demonstrated that social functioning difficulties were related to a deficit in typical somatic marker formation and therefore are neurobiological in origin. From a theoretical perspective, the findings indicate that the social components of autistic characteristics in adults with epilepsy with or without a typical developmental period may be explained by the somatic marker hypothesis. The experiments revealed a relationship between AED effectiveness and autistic characteristics, both with and without epileptic activity. Further, this thesis argues that autistic characteristics are not solely related to the medial temporal structures or a diagnosis of TLE or determined by early-onset of epilepsy. Of note, previous research demonstrating a greater risk of social cognitive deficits in MTLE patients indicate that specific epilepsy types may be a factor for severity of impairment. Importantly, the research identified that some autistic characteristics may be acquired in adulthood. Further research is needed to fully establish the extent of their heritability in the epilepsy population with reference to neuro-developmental phenotypes for TLE. Indeed, in this heterogeneous sample, there is variability in the autistic characteristics that are comparable to existing variability found in adults within the autism spectrum.

This research proposes that the social consequences of epilepsy can be cognitive in origin, and can be an under-recognised feature of this condition, even in the absence of any significant memory impairments. The focus now should be on characterising specific social and communication difficulties, and future research should aim to discriminate: i) what is genuinely related to having clinical or subclinical seizures, and ii) whether the somatic marker hypothesis has increased explanatory power before AED intervention.

Given the findings in this research project, care must be taken in future research of adults with ASD, to discriminate between those with and without epilepsy, as some autistic characteristics may be related to having a diagnosis of epilepsy or to seizure activity, but controlled by AEDs. However, consideration has to be given to ASD being a behaviourally-defined condition, in contrast to the epileptic syndromes, which are diagnosed on specific clinical symptoms and signs, supported by EEG findings. Further, rapid or atypical onset of symptoms, fluctuating symptoms or recovery is not typical of ASD, and therefore may raise suspicion of epilepsy.

It is the position of this thesis that the autism-epilepsy co-morbidity strongly indicates that the characteristics identified in this research have belonged to epilepsy for a long time, since historical evidence indicates that epilepsy has been recorded for over 2,000 years. Therefore for individuals with epilepsy and autistic characteristics, these characteristics were likely to have been present many years before assessment measures for autism spectrum disorders were first developed.

Although the aim of this research does not include an investigation of IEDs, it is the position of this thesis that IEDs in adults with epilepsy are not benign and could lead to changes in behaviour which may have negative consequences related to autistic characteristics. The literature review of the onset of epilepsy suggests that autistic characteristics may be better understood when there is consideration of the effect of epileptic discharges on brain function. Additionally, previous research evidence has demonstrated that chronic epileptic activity can have lasting implications for the development of autistic characteristics in adults with epilepsy. Replication of these experiments and further research would be valuable to improve the strength of the conclusions of this research and clarify some of the debates within this thesis.

These findings aim to benefit all people with epilepsy and those who socially interact with people with epilepsy. This will be valuable for informing healthcare professionals who develop epilepsy specialist care pathways in a variety of healthcare settings. The findings aim to improve the understanding of these characteristics in epilepsy and improving awareness of the difficulties associated with this condition. Finally, this research thesis hopes to inspire others to research autistic characteristics in adults with epilepsy in the future.

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Please read before starting

Research Aim

The objective of this pilot study is to investigate an epileptic event such as an 'aura' preceding a seizure compared with a non-epileptic event. *If you are not sure if you have an aura, please fill in the 'with aura' section from the part of the seizure that you can remember.*

Privacy

All information collected during the research shall be kept confidential and protected from unauthorised use or theft. You have the right to withdraw at any time for whatever reason, and without giving a reason.

Support

If you need further information or require any support before, during or after your participation, please contact the researcher on the number below. You will be able to discuss any feelings that arouse which may cause distress, and to give any feedback at the end of this questionnaire. All enquiries will be handled confidentially.

Instructions

The Questionnaire should be completed as near to or during an epileptic aura with an impending epileptic seizure. However, if this becomes difficult, this questionnaire can be fully completed at the next available time, as near to an epileptic aura as possible. Please read the feedback form and mail all the documents back using the envelope provided.

Filling in this questionnaire should not prevent you from making any preparations that you would normally take for an impending epileptic seizure.

*Your participation is entirely voluntary, and therefore highly valued.
Thank you for participating in this research.*

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What is an Aura?

An aura can be any symptom of epilepsy which becomes worse that is *not part of the seizure*, but can happen at any time. For some individuals it can indicate the start of their seizure.

If you are not sure if you have an aura, please fill in the 'with aura' section from the part of the seizure that you can remember.

*Below are some differences you may notice only during an aura.
Please tick whether these apply to you:*

Your name: _____

Social Communication: ☐ Decreased ability to speak ☐ Decreased ability to respond to others
☐ Decreased ability to sustain a conversation ☐ Decreased ability to make eye contact with others

Social Interaction: ☐ Increased level of concentration ☐ Increased avoidance of people
☐ Increased inability to understand others ☐ Increased level of self-introversion

Imagination: ☐ Inability to perform something new ☐ Inability to remember past events
☐ Inability to do something spontaneously ☐ Inability to predict intentions of others
☐ Inability to consider options ☐ Inability to make decisions

Perception: ☐ Increased visual sensitivity ☐ Increased hearing sensitivity ☐ Increased touch sensitivity
☐ Increased smell sensitivity ☐ Increased difficulties with visual movement
☐ Altered relationship between self and environment ☐ Altered perception of whole environment

Emotion: ☐ Joy ☐ Depression ☐ Sadness ☐ Anger ☐ Euphoria
☐ Anxiety ☐ Fear

Questionnaire

How to fill out the questionnaire

Below are a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer. Please rate whether this decreases, stays the same, or increases during an Aura or part of the seizure which you can remember, by circling your answer in the right hand column marked WITH AURA.

DO NOT MISS ANY STATEMENT OUT.

Examples

	WITHOUT AURA					WITH AURA		
E1. I am willing to take risks.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases
E2. I like playing board games.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases
E3. I find learning to play musical instruments easy.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases

START HERE.

	WITHOUT AURA					WITH AURA		
1. I prefer to do things with others rather than on my own.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases
2. I prefer to do things the same way over and over again.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases
3. If I try to imagine something, I find it very easy to create a picture in my mind.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases
4. I frequently get so strongly absorbed in one thing that I lose sight of other things.	definitely agree	slightly agree	slightly disagree	definitely disagree		decreases	stays same	increases

WITHOUT AURA

WITH AURA

5. I often notice small sounds when others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
6. I usually notice car number plates or similar strings of information.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
8. When I'm reading a story, I can easily imagine what the characters might look like.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
9. I am fascinated by dates.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
10. In a social group, I can easily keep track of several different people's conversations.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
11. I find social situations easy.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
12. I tend to notice details that others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
13. I would rather go to a library than a party.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
14. I find making up stories easy.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
15. I find myself drawn more strongly to people than to things.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
16. I tend to have very strong interests which I get upset about if I can't pursue.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
17. I enjoy social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>

WITHOUT AURA

WITH AURA

18. When I talk, it isn't always easy for others to get a word in edgeways.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
19. I am fascinated by numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
20. When I'm reading a story, I find it difficult to work out the characters' intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
21. I don't particularly enjoy reading fiction.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
22. I find it hard to make new friends.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
23. I notice patterns in things all the time.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
24. I would rather go to the theatre than a museum.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
25. It does not upset me if my daily routine is disturbed.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
26. I frequently find that I don't know how to keep a conversation going.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
27. I find it easy to "read between the lines" when someone is talking to me	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
28. I usually concentrate more on the whole picture, rather than the small details.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
29. I am not very good at remembering phone numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
30. I don't usually notice small changes in a situation, or a person's appearance.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>

WITHOUT AURA

WITH AURA

31. I know how to tell if someone listening to me is getting bored.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
32. I find it easy to do more than one thing at once.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
33. When I talk on the phone, I'm not sure when it's my turn to speak.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
34. I enjoy doing things spontaneously.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
35. I am often the last to understand the point of a joke.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
36. I find it easy to work out what someone is thinking or feeling just by looking at their face.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
37. If there is an interruption, I can switch back to what I was doing very quickly.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
38. I am good at social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
39. People often tell me that I keep going on and on about the same thing.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
40. When I was young, I used to enjoy playing games involving pretending with other children.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
42. I find it difficult to imagine what it would be like to be someone else.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>

WITHOUT AURA

WITH AURA

43. I like to plan any activities I participate in carefully.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
44. I enjoy social occasions.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
45. I find it difficult to work out people's intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
46. New situations make me anxious.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
47. I enjoy meeting new people.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
48. I am a good diplomat.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
49. I am not very good at remembering people's date of birth.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>
50. I find it very easy to play games with children that involve pretending.	definitely agree	slightly agree	slightly disagree	definitely disagree		<i>decreases</i>	<i>stays same</i>	<i>increases</i>

Thank you for filling this questionnaire in.

Developed by:
The Autism Research Centre
University of Cambridge

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Feedback Form

Thank you for your participation in this study. Please use this form to give any feedback to the researcher about your experience of this research. If you wish to discuss any feelings that arouse during this study which may cause distress, please use the feedback form below or contact the researcher. All enquiries will be handled confidentially.

Please use this area to provide feedback on this research:

Thank you for filling in this feedback form.

Group A

Instructions

Do Booklet 2 *First*

Do Booklet 3 *Second*

Please read before starting

Research Aim

The aim of this study is to investigate cognition and behaviour in individuals with epilepsy with and without an aura. Please complete the Personal details page and read the instructions.

Support

If you need further information or require any support before, during or after your participation, please contact the researcher on the number below. You will be able to discuss any feelings that arouse which may cause distress, and to give any feedback at the end of this questionnaire.

Privacy

All information collected during the research shall be kept confidential and protected from unauthorised use or theft. You have the right to withdraw at any time for whatever reason, and without giving a reason.

Your participation is entirely voluntary, and therefore highly valued.

Thank you for participating in this research.

All enquiries to SallyAnn Wakeford : **01225 384523**

Email: **srw22@bath.ac.uk**

All enquiries will be handled confidentially.

Personal Details

Name: _____ Today's Date: _____

Address: _____

Date of birth: _____ (*over 18 years old only*) Sex: M / F

Frequency of seizures: daily / weekly / monthly / yearly / other _____

How well are your seizures controlled by medication? [*1=Poorly controlled, 5=Well controlled*]

(Please circle): **1** **2** **3** **4** **5**

Have you currently changed the medication to control your seizures? YES / NO

If so, when: _____

What is an Aura?

An aura can be any symptom of epilepsy which becomes worse that is *not part of the seizure*, but can happen at any time. For some individuals it can indicate the start of their seizure.

Instructions

Please complete **Booklet 2** *only* during an aura or on a day when you are having a lot of aura activity throughout the day, and having symptoms from your epilepsy.

1. Complete Booklet 2 during an aura **FIRST**
2. Complete Booklet 3 without an aura **SECOND**
3. Please mail all the documents back using the envelope provided
4. Complete the feedback form if you wish, thank you.

Booklet 1

Please do first - during a seizure aura

Instructions

For each set of eyes, choose and circle which word best describes what the person in the picture is thinking or feeling. You may feel that more than one word is applicable but please choose just one word, the word which you consider to be most suitable.

Before making your choice, make sure that you have read all 4 words.

You should try to do the task as quickly as possible but you will not be timed. If you really don't know what a word means you can look it up in the definition list at the end.

practice

jealous

panicked



arrogant

hateful

1

playful

comforting



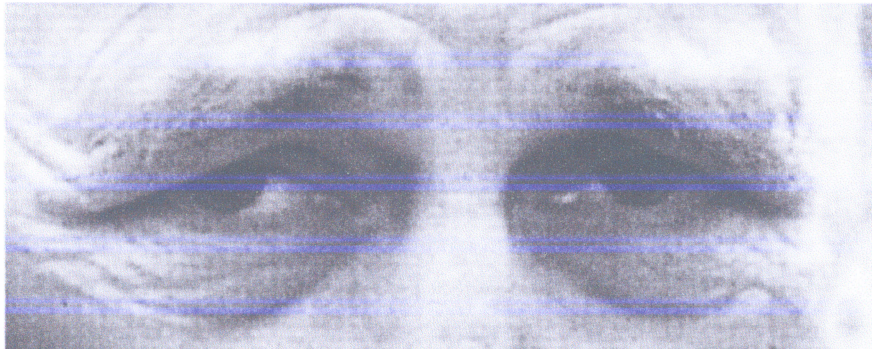
irritated

bored

2

terrified

upset



arrogant

annoyed

3

joking

flustered



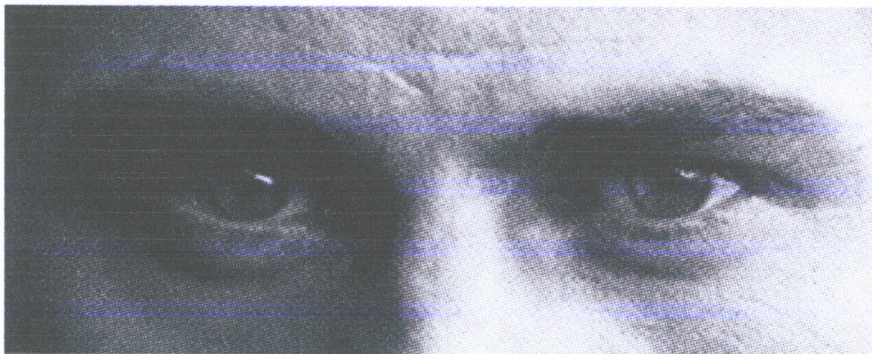
desire

convinced

4

joking

insisting



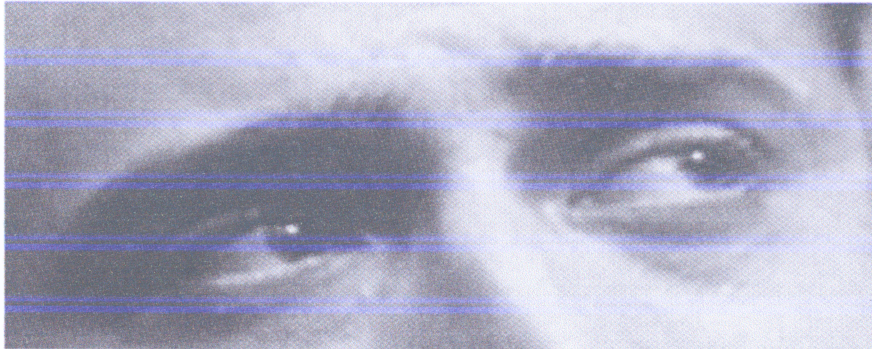
amused

relaxed

5

irritated

sarcastic



worried

friendly

6

aghast

fantasizing



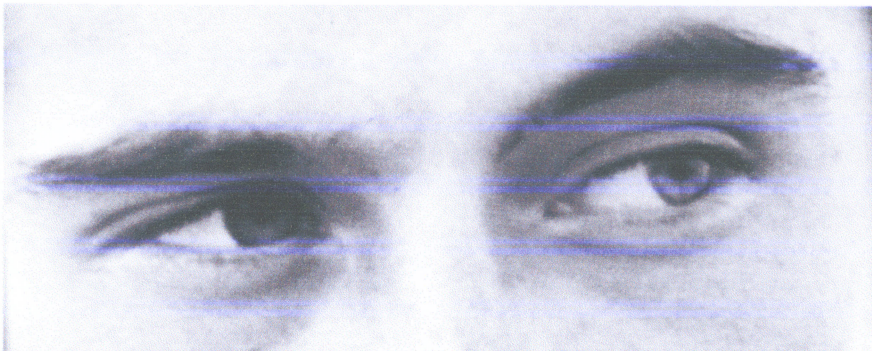
impatient

alarmed

7

apologetic

friendly



uneasy

dispirited

8

despondent

relieved



shy

excited

annoyed

hostile



horrified

preoccupied

10

cautious

insisting



bored

aghast

terrified

amused



regretful

flirtatious

12

indifferent

embarrassed

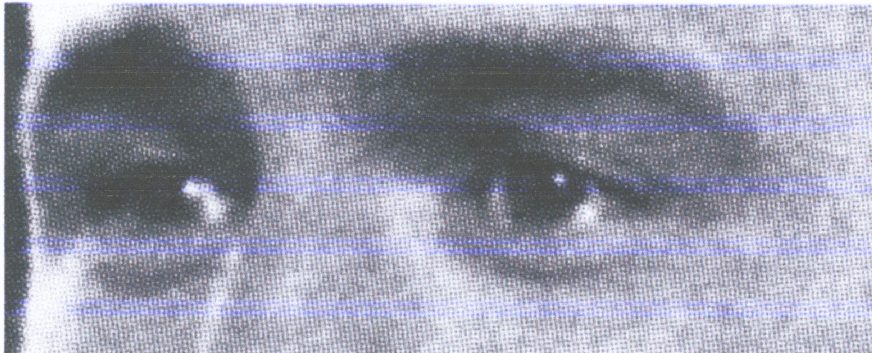


sceptical

dispirited

decisive

anticipating



threatening

shy

irritated

disappointed



depressed

accusing

15

contemplative

flustered



encouraging

amused

irritated

thoughtful



encouraging

sympathetic

17

doubtful

affectionate



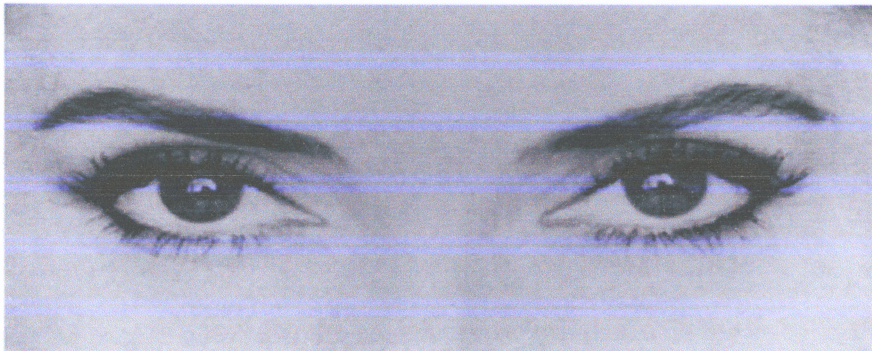
playful

aghast

18

decisive

amused



aghast

bored

Instructions

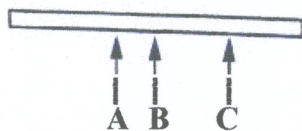
This section aims to find out whether you can easily understand how things work and function.

Each question has a diagram by it, from which the answer can be worked out. After each question there is a choice of answers. Only one is correct.

When you think you have found the correct answer, please indicate your choice by putting a circle around it. An example is shown below.

This section should not take any more than 5 minutes. Please try to answer all the questions as quickly and as accurately as you can, and then enter the *total time taken to complete this section* in the box at the end.

Example:



Which arrow will balance the beam?
(a) A (b) B (c) C (d) all equal

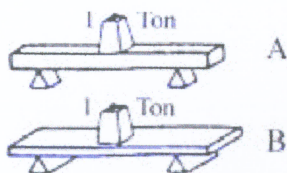
Now please enter start time, and begin.

Enter Start time now :

The time is:

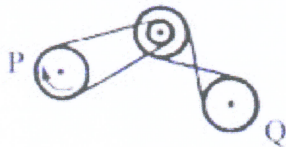
START HERE.

11.



Which plank is more likely to break?
(a) A (b) B (c) either

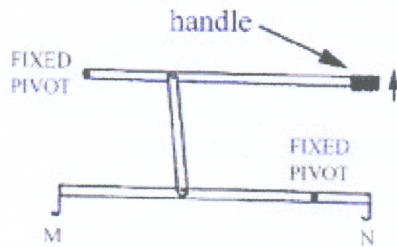
12.



Which way will wheel Q turn when wheel P rotates as shown?

- (a) (b) (c) either

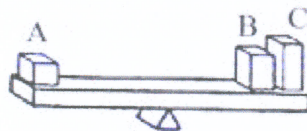
13.



If the handle is moved as shown, how will the hooks M and N move?

- (a) M up, N down
(b) M down, N up
(c) M up, N up
(d) M down, N down
(e) M up, N still

14.



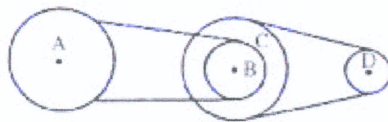
Which box is the heaviest?

- (a) A (b) B (c) C (d) all equal

15.

The diameter of pulleys A and C is 10cm and the diameter of pulleys B and D is 5cm. When pulley A makes a complete turn, pulley D will turn

- (a) once (b) twice (c) 4 times (d) 6 times (e) 8 times

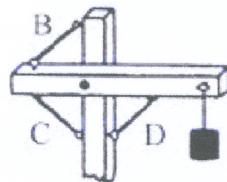


16.

If pulley D is the driver, (i.e. pulley D rotates) which pulley turns slowest?

- (a) A (b) B (c) C (d) all the same

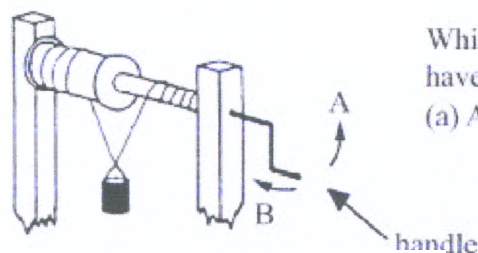
17.



Which chain would support the weight by itself?

- (a) any equally (b) B (c) C (d) D

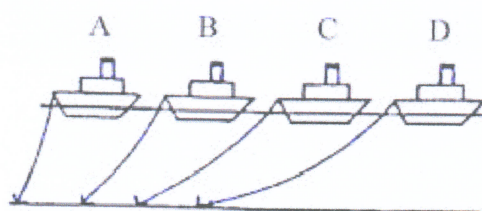
18.



Which way would the handle have to turn to raise the bucket?

- (a) A (b) B (c) either

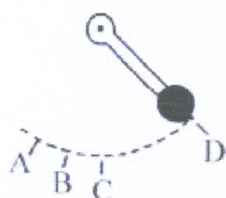
19.



Which boat has the safest anchorage?

- (a) A (b) B (c) C (d) D

20.



Where is the pendulum moving fastest?

- (a) A (b) B (c) C (d) D

NOTE THE TIME AT THIS POINT

Time taken to complete this section

mins

secs

Debriefing Notes

Thank you for your participation in this task. This research task investigates the way that individuals with epilepsy think and behave.

The aim of the research is to investigate how people with epilepsy process social information, and whether epilepsy affects the way people recognise the emotions of others. This research also investigates the way people with epilepsy think with and without seizure aura's, to uncover the hidden difficulties that people with epilepsy have, and the impact this has on daily life.

The researcher has provided a feedback form which you can complete now, if you wish to use this opportunity to discuss any issues. All of your information will be handled confidentially.

Feedback Form

Thank you for your participation in this study. Please use this form to give any feedback to the researcher about your experience of this research, or to discuss any feelings that arouse during this study which may cause distress. All enquiries will be handled confidentially.

Please use this area to provide feedback on this research:

Thank you for filling in this feedback form.

Post to: SallyAnn Wakeford
Department of Psychology, University of Bath
FREEPOST RRAU-ZELZ-ZEZK
Bath BA2 7AY
Email: srw22@bath.ac.uk
Tel: 01225 386523

Study Title:

Developing an epilepsy-specific questionnaire

Study web link:

www.surveymonkey.com/s.aspx?sm=Bk25EZBkl2_2fyKrg9AXX_2fDQ_3d_3d

Researcher/s and associated university: SallyAnn Wakeford, University of Bath,
srw22@bath.ac.uk

Study category: Cognition in Epilepsy

Brief description of study:

SallyAnn Wakeford, a PhD student at the University of Bath, would like to hear from adults with epilepsy who would be willing to complete a questionnaire which investigates how epilepsy affects the way we think and behave. The research aims to develop an epilepsy-specific way of measuring cognitive and behavioural abilities. People with epilepsy need special consideration with psychological testing, and current tests are not developed especially for those with epilepsy. Improvements to all standard psychological tests can enhance a real understanding of epilepsy and will benefit all people with epilepsy, by improving what treatments are offered.

Country residence of principle researcher: England, UK

Please read before starting

Research Aim

The aim of the research is to investigate how people with epilepsy process social information and whether epilepsy affects the way people think and behave. This research also investigates the way people with epilepsy think with and without seizure aura's, to uncover the hidden difficulties that people with epilepsy have, and the impact this has on daily life.

Privacy

All information collected during the research shall be kept confidential and protected from unauthorised use or theft. You have the right to withdraw at any time for whatever reason, and without giving a reason.

Support

If you need further information or require any support before, during or after your participation, please contact the researcher on the number below. All enquiries will be handled confidentially.

For all enquiries please contact:

SallyAnn Wakeford Telephone: 01225 384349
Email: srw22@bath.ac.uk

Postal Address: SallyAnn Wakeford
Department of Psychology
University of Bath
FREEPOST RRAU-ZELZ-ZEZK
Bath BA2 7AY

Personal Details

Name: _____ Today's Date: _____

Address: if you would like to be contacted again (*to participate in further research*):

Date of epilepsy onset: _____ Sex: M / F

Date of birth: _____ *You must be over 18 years old to participate.*

How often do your seizures occur: _____

When was your last seizure: _____

Do you have temporal lobe epilepsy, *if not please specify*: _____

What if any is the known cause of your epilepsy, *please specify*: _____

Are you currently taking anti-epileptic or other medication to control your seizures? YES / NO

Have you ever been diagnosed with the following (please tick):

☐ Autism ☐ Asperger Syndrome

☐ Other Autism Spectrum Disorders, *please specify*: _____

Have you changed any medication in the last two months? _____

Instructions

Please enter a response for the following 11 questions, by thinking about how true each statement is of you when you are experiencing or not experiencing a 'Seizure Aura'.

An aura can be any symptom of epilepsy that you are aware of, that is not part of the seizure itself. For some individuals it can indicate the start of their seizure.

*Your participation is entirely voluntary, and therefore highly valued.
Thank you for participating in this research.*

Scoring

Please rate your behaviour for each of the statements below, and indicate how true you think each statement is for you. There are no right or wrong answers. Please be as honest as you can and answer all the questions you are able to.

Use these definitions to score each item:

0: False, not at all true

1: Slightly true

2: Mainly true

3: Very true

	<i>Without Aura</i>	<i>With Aura</i>
I avoid eye contact with other people		
I have difficulty making friends, even when trying my best		
I am sometimes regarded by other people as odd or weird		
I have trouble keeping up with the flow of normal conversation		
I have difficulty relating to peers		
Compared to others, I have a restricted or unusually narrow range of interests		
I have trouble understanding the meaning of other people's tone of voice and facial expressions		
I have trouble concentrating too much on parts of things rather than seeing the whole picture		
I have more difficulty than others do with changes in routine		
I would rather be alone than with others		
I am (or used to be) overly sensitive to sounds, textures or smells		

Feedback Form

Thank you for your participation in this study. Please use this form to give any feedback to the researcher about your experience of this research. If you wish to discuss any feelings that arouse during this study which may cause distress, please use the feedback form below or contact the researcher. All enquiries will be handled confidentially.

Please use this area to provide feedback on this research:

Thank you for filling in this feedback form.

Please read before starting

Research Aim

The aim of the research is to investigate how people with epilepsy process social information and whether epilepsy affects the way people think and behave. This research also investigates the way people with epilepsy think with and without seizure aura's, to uncover the hidden difficulties that people with epilepsy have, and the impact this has on daily life.

Privacy

All information collected during the research shall be kept confidential and protected from unauthorised use or theft. You have the right to withdraw at any time for whatever reason, and without giving a reason.

Support

If you need further information or require any support before, during or after your participation, please contact the researcher on the number below. All enquiries will be handled confidentially.

For all enquiries please contact:

SallyAnn Wakeford Telephone: 01225 384349
Email: srw22@bath.ac.uk

Postal Address: SallyAnn Wakeford
Department of Psychology
University of Bath
FREEPOST RRAU-ZELZ-ZEZK
Bath BA2 7AY

Personal Details

Name: _____ Today's Date: _____

Address: if you would like to be contacted again (*to participate in further research*):

Date of epilepsy onset: _____ Sex: M / F

Date of birth: _____ *You must be over 18 years old to participate.*

How often do your seizures occur: _____

When was your last seizure: _____

Do you have temporal lobe epilepsy, *if not please specify*: _____

What if any is the known cause of your epilepsy, *please specify*: _____

Are you currently taking anti-epileptic or other medication to control your seizures? YES / NO

Have you ever been diagnosed with the following (please tick):

☐ Autism ☐ Asperger Syndrome

☐ Other Autism Spectrum Disorders, *please specify*: _____

Have you changed any medication in the last two months? _____

Instructions

Please enter a response for the following 12 questions, by thinking about how true each statement is of you when you are experiencing or not experiencing a 'Seizure Aura'.

An aura can be any symptom of epilepsy that you are aware of, that is not part of the seizure itself. For some individuals it can indicate the start of their seizure.

*Your participation is entirely voluntary, and therefore highly valued.
Thank you for participating in this research.*

Scoring

Please rate your behaviour for each of the statements below, and choose the score that best describes the extent of the problem for you. There are no right or wrong answers. Please be as honest as you can and answer all the questions you are able to. The first 3 items refer to specific situations (i.e. travelling, leisure time and communicating) and examples are provided in brackets. The remaining 9 items refer to how problematic you feel these behaviours are for you generally.

Use these definitions to score each item:

- 0: Absent**, behaviour does not occur
- 1: Mild**, behaviour occurs and is a mild problem
- 2: Moderate**, behaviour occurs and is a moderate problem
- 3: Severe**, behaviour occurs and is a severe problem

	<i>Without Aura</i>	<i>With Aura</i>
TRAVEL: (Insist on taking certain routes/paths; Must sit in specific location in vehicles; Insist that certain items be present during travel; Insist on seeing or touching certain things or places during travel such as a sign or store).		
LEISURE PROBLEMS: (Insist on certain leisure activities; Follow a rigid routine during leisure; Insist that certain items be present/available during leisure; Insist that other persons do certain things during play/leisure).		
SOCIAL INTERACTIONS: (Insist that others say certain things or respond in certain ways during interactions; Repeat same topic(s) during social interactions; Repetitive questioning; Insist on certain topics of conversation).		
Object to visiting new places		
Become upset if interrupted in what you are doing		
Insist on walking in a particular pattern (e.g., straight line)		
Insist on sitting at the same place		
Not comfortable with changes in appearance or behaviour of the people around you		
Insist on using a particular door		
Resist changing activities; Difficulty with changes		
Insist on the same routine, household, study or work schedule		
Insist that specific things take place at specific times		

Feedback Form

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Please use this area to provide feedback on this research:

Thank you for filling in this feedback form.

Consent Form

1. Study Title

Cognition and behaviour in adults with epilepsy.

2. Invitation Paragraph

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with the researcher. Please ask if there is anything that is not clear, or if you would like more information.

3. What is the purpose of this study?

These studies investigate memory patterns, visuo-perceptual processing skills and social cognition in adults with and without epilepsy. The purpose of the memory studies are to investigate if a model can be provided to enhance memory recall.

4. Why have I been chosen?

You are a volunteer and can decide whether or not to take part. We are looking for adults aged over 18 who do not have a diagnosis of any autism spectrum disorder. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. At any time during this research, you are still free to withdraw at any time, without giving a reason.

5. What will happen

The study will take approximately 90 minutes to complete. After reading this information and giving your written consent you will be asked to carry out a series of tasks which investigates cognitive processing. You will be able to take breaks between tasks, or withdraw at any time. At the end of the tasks, you will be given more information about this research.

6. What do I have to do?

The researcher will take you through each task, but if there is anything that you need, or if you feel unwell at any time, please let the research know.

7. What are the side effects of taking part?

There are no negative effects anticipated with any of these tasks, and the researcher will be with you at all times to assist you.

8. What are the possible benefits of taking part?

You will receive a £5 voucher or a box of chocolates in exchange for your time. Lunch will be provided, and bottled water is available. A travel refund is also available up to £50 for return travel to the University of Bath.

9. Will my taking part in this study be kept confidential?

All information that is collected about you during the research will be kept strictly confidential, and no information collected will have your name or any other means of identifying you personally, so that you will remain anonymous.

Consent Form (cont.)

10. What will happen to all the information after the study?

All data collected will be kept secure and will not identify you in anyway. The data will continue to be protected by a unique code number rather than your name, and will be protected at all times from unauthorised use or theft.

11. What will happen to the results of the research study?

The results of the research will be freely disseminated through supporting charities and other suitable organizations. The results will be available to all participants who take part in the research.

12. Who is organizing and funding the research?

The study is being organised by SallyAnn Wakeford, a PhD student in the Department of Psychology at the University of Bath. The research has non-financial support from Epilepsy Action and The National Society for Epilepsy. The research is funded by SallyAnn Wakeford.

13. Who has reviewed this study?

This research has been reviewed and approved by the Department of Psychology Ethical Committee at University of Bath, (*reference numbers 10-745; 10-746; 10-747*).

14. Contact for further information

Your contact for further information is: SallyAnn Wakeford, Department of Psychology, University of Bath, BATH, BA2 7AY. Tel. 01225 384 349. email: srw22@bath.ac.uk

To be completed by the participant

I have read and understood the information sheet provided about the purpose of the research. I have understood the information and I know that I can withdraw at any time during the research, for whatever reason and without giving a reason.

Name _____

Signature _____ Date _____

Please note that you will be given a copy of the information sheet and a signed consent form to keep.

Results

Study 1, Autism Quotient

Study 1 revealed that participants with epilepsy revealed increased attention-to-detail, and reduced imagination, social skills, communication and attention-switching, than the non-epilepsy participants, and these last three abilities reduced again during a seizure aura.

Study 2, Adult Eyes-Revised and the Intuitive Physics Task

Study 2a revealed that there was no difference in identification of emotional expression on the faces of others between adults with epilepsy and without epilepsy. Study 2b revealed that there was no difference in systemising abilities adults with epilepsy and without epilepsy, however this ability reduced during a seizure aura.

Study 3, Social Responsiveness Scale-short

Study 3 revealed that participants with epilepsy scored lower for social responsiveness than the non-epilepsy participants, and these scores were lower again during a seizure aura.

Study 4, Repetitive Behavior Scale-Revised, short

Study 4 revealed that participants with epilepsy do not differ in their repetitive behaviours to those without epilepsy. Participants with epilepsy without current seizures revealed less repetitive behaviours than those with current seizures.

Study 5, GEFT

Study 5 revealed that there was no difference in performance in identifying simple shapes embedded in a larger complex picture, between those with and without epilepsy.

Study 6. Memory Tasks

Study 6a revealed that there was no difference between those with and without epilepsy when recalling unrelated and related words. Study 6b revealed that there was no difference in recall of words between those with and without epilepsy.

Study 7. Adult Eyes-Revised

Study 7 revealed that there was no difference of correct identification and rating of emotional expression on the faces of others between those with and without epilepsy.

Study 8. IOWA task

Study 8 revealed that there was no difference in the overall amount of money won or lost between those with and without epilepsy. However, a difference of slower learning at the beginning of the task and faster learning at the end of the task was demonstrated by the epilepsy group.

Experiment 5a

I am now going to read out a list of words when you are ready.

Please listen carefully to all the words. When I have finished reading from this list I will look up towards you and when you see this, I would like you to immediately tell me all the words that you can remember. You can have as much time as you like to remember the words.

I am now going to repeat these instructions. [repeat]

Do you understand the instructions? [acknowledgement]

Please let me know when you are ready to start by saying “GO” and I will begin to read the list.

Experiment 5a

<u>Group A</u> <u>Unrelated [UWL]</u>	<u>Group B</u> <u>Related [RWL]</u>
APPLE	BEAR
PARCEL	RABBIT
SHIRT	GIRAFFE
HOUSE	HORSE
DRUM	MOUSE
LAMP	LION
PENCIL	COW
ONION	PIG
POT	TURTLE
AIRPLANE	RACCOON
THUMB	SHEEP
BROWN	MONKEY

Experiment 5b

Study Phase

I am now going to show you some words one at a time for about 5 seconds. Please look carefully at all the words. If I show you a card with no letters missing: like this [show example card], I would like you to read the word and then say the word aloud to me. If the word has letters missing like this [show example card], I would like you to read the clue underneath to yourself, and then say the word aloud to me. Do you have any questions?

Filler Task

There will now be two short tasks, and afterwards I will give you a memory test. For this first task, I would like to give you this sheet for you to copy the correct symbol using the key above underneath each number.

Test Sheet 1

“Thank you, I’d like to give you this sheet and ask you to fill it in before I give you the memory test. Please can you work quickly to complete as many of these words as you can **with the first word that comes to mind**, without using any proper nouns - words such as the name of a person or a specific place, John, Birmingham, for example, so just the **first word that comes to your mind**. Do you have any questions?”

Test Sheet 2

Thank you. I would like to ask you to take this memory test. Please use the initial letters to remind you of the words that you studied earlier. Only half of these words were shown to you, so please try not to guess any of the words for this test. Do you have any questions?

Practice Example Cards

MANTLE

S _____

A small dish underneath a cup

STUDY LIST A [x40]

Generate x20 / Read x20

ORANGE	Red dish yellow citrus fruit
TONGUE	Organ of taste in mouth
LADDER	A set of rungs between uprights used for climbing up
FLOWER	Part of a plant where a fruit or seed develops
JUNGLE	A tropical forest
PYTHON	A large snake that crushes its prey
FINGER	Each of the five parts extending from each hand
NEPHEW	The son of a brother or sister
PARCEL	Something wrapped in paper for posting
DINNER	An evening meal, or main meal
TEAPOT	Tea and teabags are brewed in it
SOCCER	Another name for English football
PALLET	An artist's board to mix colours
SQUARE	A shape with four sides
FARMER	Someone who grows vegetables and raises animals for a living
KITTEN	A young cat
LETTER	A written message sent by post in an envelope
DESERT	A dry arid place with sand and dunes
BUCKET	A vessel used for carrying water
CAMERA	An object used for taking photographs

HICCUP
ANORAK
TROUGH
MARBLE
TONSIL
RODENT
STOREY
COWBOY
RABBIT
WIZARD
NATURE
POISON
MILLER
LOUNGE
HOOVER
GEYSER
SIGNAL
DRAWER
CUCKOO
BEETLE

STUDY LIST B [x40]

Generate x20 / Read x20

FRIEND	The opposite of enemy
STABLE	Building in which horses are kept
POTATO	A vegetable used for making chips
THREAD	A strand of cotton
ROCKET	A missile fired into space
HERMIT	A solitary monk
GARDEN	Where vegetables and flowers grow
THRONE	The Queens royal seat
WALNUT	A nut used in salads and cakes
GROCER	Shopkeeper selling fruit and vegetables
COLLAR	The part of a shirt that buttons around the neck
BUTTER	A spread for bread, made from cow's milk
MAGNET	A piece of metal that attracts iron filings and points north when suspended
SCHOOL	A place where children are educated
CINEMA	A theatre where films are shown
FRIDGE	An appliance to keep food cold
MIRROR	A piece of coated glass in which a reflection can be seen
PULPIT	A raised platform in a church from which a preacher speaks
KENNEL	A place where dogs are kept
BOTTLE	A container with a narrow neck used for holding liquid

CRAYON
LENTIL
LAPTOP
GINGER
HORNET
TUNNEL
SPONGE
NOBODY
ARMOUR
LOCUST
COPPER
SHROUD
CLOVER
SLEDGE
BARROW
STRING
LAWYER
CACTUS
GIBBON
BASKET

List 1

Name _____ **Test** _____

ORA _ _ _	CRA _ _ _
TON _ _ _	LEN _ _ _
LAD _ _ _	LAP _ _ _
FLO _ _ _	GIN _ _ _
JUN _ _ _	HOR _ _ _
PYT _ _ _	TUN _ _ _
FIN _ _ _	SPO _ _ _
NEP _ _ _	NOB _ _ _
PAR _ _ _	ARM _ _ _
DIN _ _ _	LOC _ _ _
COL _ _ _	NAT _ _ _
BUT _ _ _	POI _ _ _
MAG _ _ _	MIL _ _ _
SCH _ _ _	LOU _ _ _
CIN _ _ _	HOO _ _ _
FRI _ _ _	GEY _ _ _
MIR _ _ _	SIG _ _ _
PUL _ _ _	DRA _ _ _
KEN _ _ _	CUC _ _ _
BOT _ _ _	BEE _ _ _

List 2

Name _____ **Test** _____

FRI_ _ _	HIC_ _ _
STA_ _ _	ANO_ _ _
POT_ _ _	TRO_ _ _
THR_ _ _	MAR_ _ _
ROC_ _ _	TON_ _ _
HER_ _ _	ROD_ _ _
GAR_ _ _	STO_ _ _
THR_ _ _	COW_ _ _
WAL_ _ _	RAB_ _ _
GRO_ _ _	WIZ_ _ _
TEA_ _ _	COP_ _ _
SOC_ _ _	SHR_ _ _
PAL_ _ _	CLO_ _ _
SQU_ _ _	SLE_ _ _
FAR_ _ _	BAR_ _ _
KIT_ _ _	STR_ _ _
LET_ _ _	LAW_ _ _
DES_ _ _	CAC_ _ _
BUC_ _ _	GIB_ _ _
CAM_ _ _	BAS_ _ _

Digit Symbol—Coding

1	2	3	4	5	6	7	8	9
—	⊥	≡	⌒	⌒	○	∨	×	=

Sample Items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

Experiment 6

1. There are 36 pictures of people's faces shown in this task.
2. I would like you to rate which emotional expression is shown by marking these boxes as shown in this first example here [point to choice of emotions]
3. Then I would like you to decide how strong you feel the emotion of the facial expression is.
4. Please rate between 0% for no emotion and 100% for Very Strong emotion by putting a line through this horizontal line here [point to scale].
5. If you rate the face as neutral just tick this box here and you need not use the scale below.
6. Do you have any questions?

Please begin.

Faces Task

Name: _____ Date of Birth: _____

Instructions

Below are 36 pictures of peoples' faces. Please rate the emotional expression and then rate how strong you feel the emotion of the facial expression is, on the scale provided. Please take as much time as you need.

1. Tick the emotion box which you think the picture shows.
2. Rate the percentage of emotion from by putting a line between 0%-100%, unless you have selected 'NEUTRAL' for faces which you rate as having no emotion.

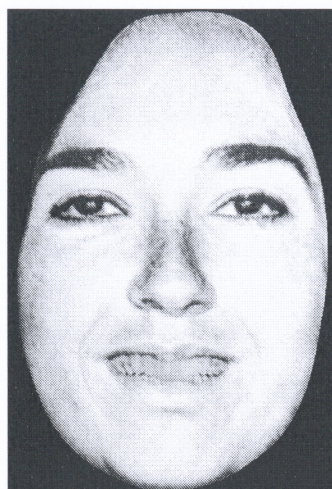


Example

☒ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

Start Here

Face 1



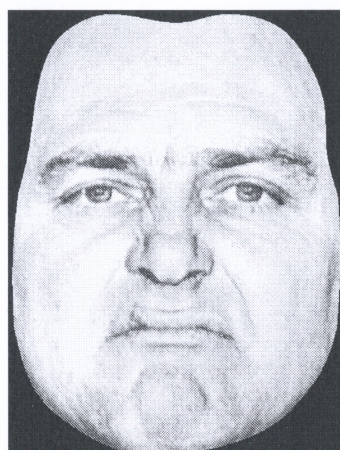
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0% 100%

Face 2



- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

Face 3



- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0% 100%



Face 4

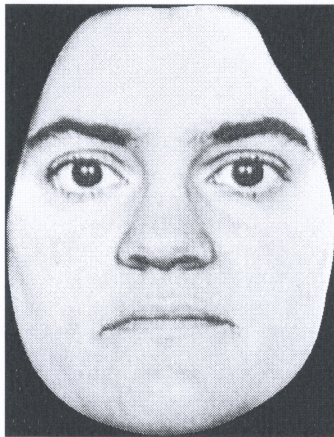
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%



Face 5

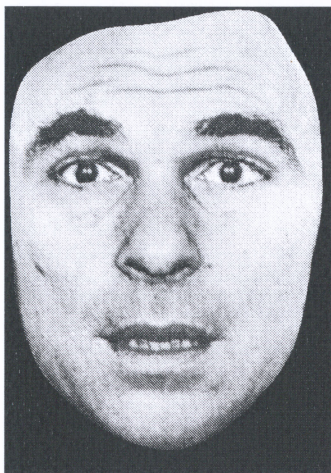
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
- ☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%



Face 6

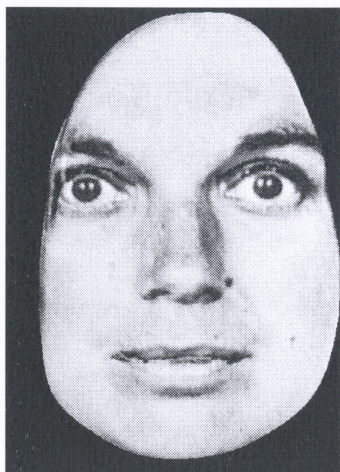
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%



Face 7

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

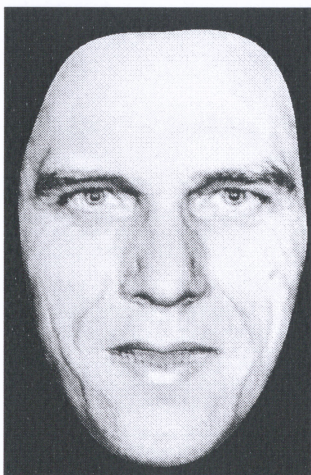


Face 8

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong



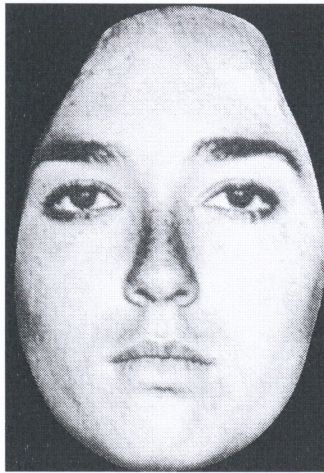
Face 9

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong





Face 10

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

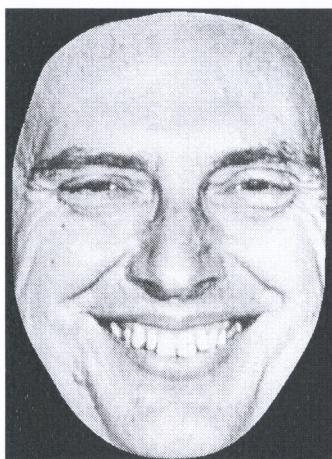
No Emotion Very Strong
|-----|
0% 100%



Face 11

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion Very Strong
|-----|
0% 100%



Face 12

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion Very Strong
|-----|
0% 100%



Face 13

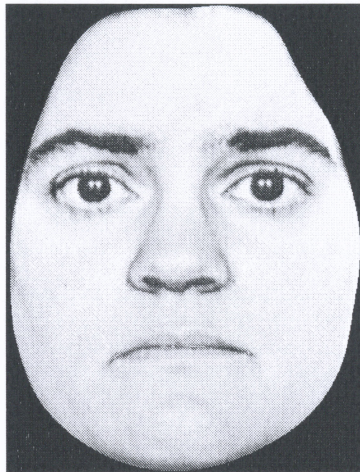
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%



Face 14

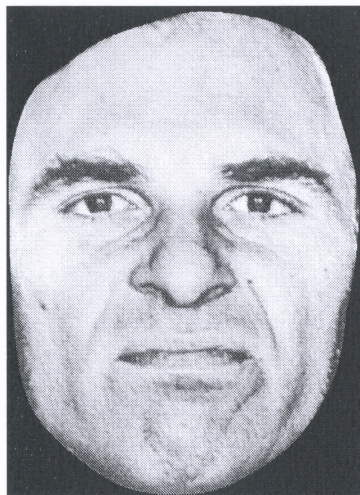
- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%



Face 15

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

0%

100%

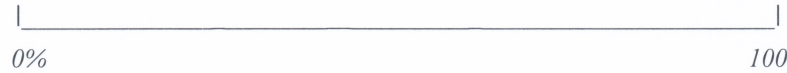


Face 16

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

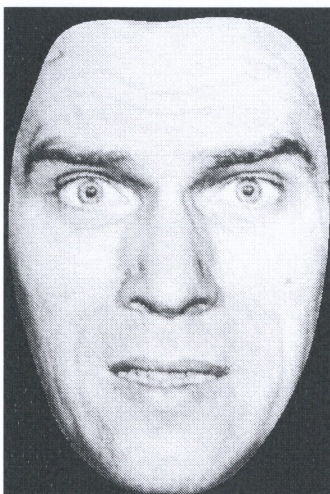


Face 17

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong



Face 18

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong





No Emotion Very Strong

0% 100%



No Emotion Very Strong

0% 100%



No Emotion Very Strong

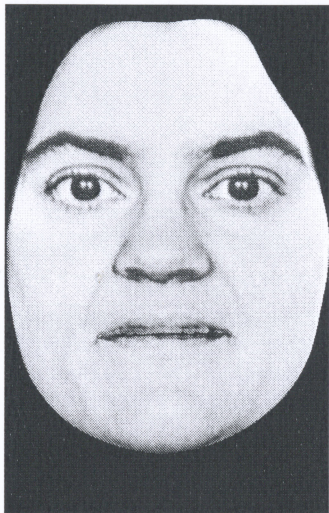
0% 100%



Face 22

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

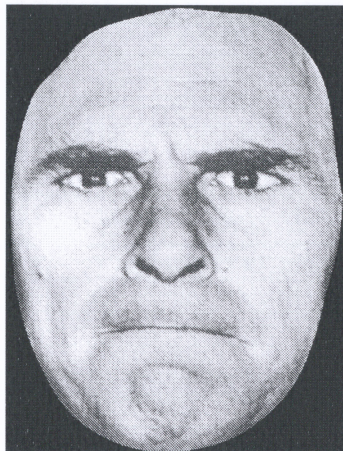
No Emotion Very Strong
|_____|
0% 100%



Face 23

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion Very Strong
|_____|
0% 100%



Face 24

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion Very Strong
|_____|
0% 100%

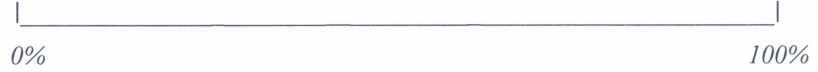


Face 25

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

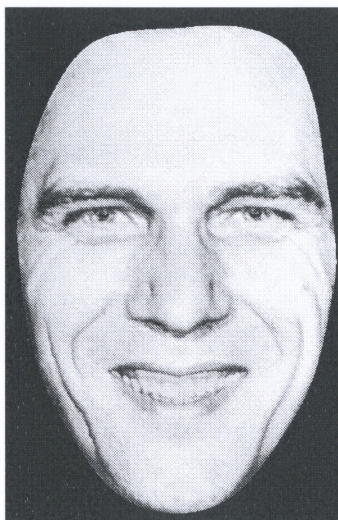


Face 26

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

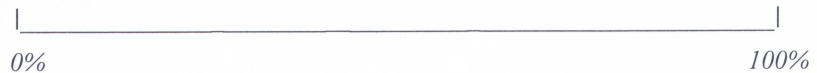


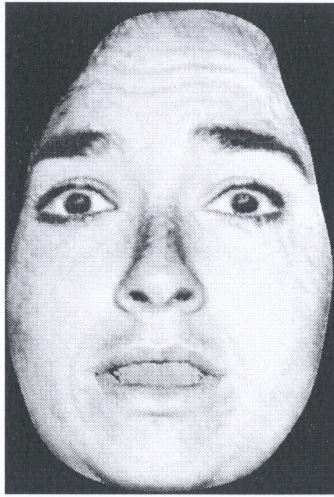
Face 27

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong





Face 28

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong



0%

100%



Face 29

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong



0%

100%



Face 30

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

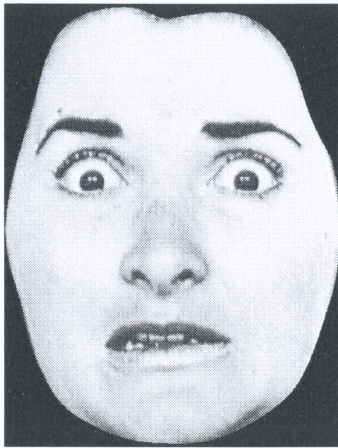
No Emotion

Very Strong



0%

100%



Face 31

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

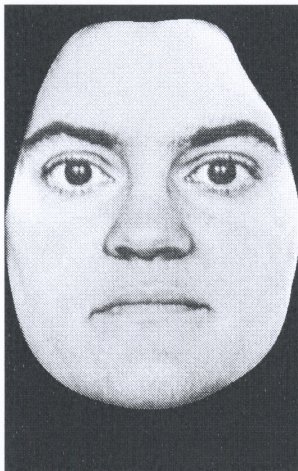
No Emotion

Very Strong

|_____|

0%

100%



Face 32

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

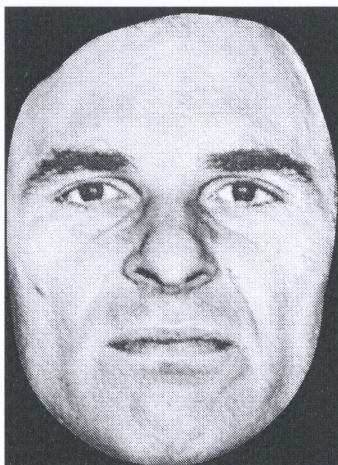
No Emotion

Very Strong

|_____|

0%

100%



Face 33

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

|_____|

0%

100%



Face 34

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

|_____|

0%

100%



Face 35

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

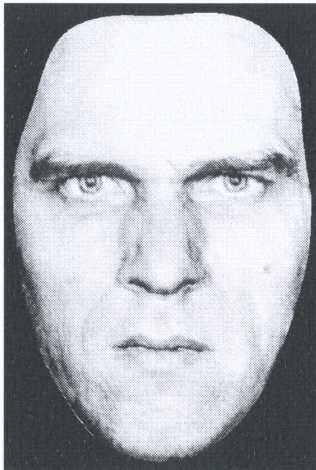
No Emotion

Very Strong

|_____|

0%

100%



Face 36

- ☐ Happiness ☐ Fear ☐ Surprise ☐ Anger
☐ Disgust ☐ Sadness ☐ Neutral

No Emotion

Very Strong

|_____|

0%

100%

Finish. Thank you for your participation in this study.

Source: The University of Manchester Faces Task, adapted from Ekman & Friesen (1976)

Experiment 7 Instructions

[Researcher displays the task interface]

1. In front of you on the screen, there are four decks of cards, 1,2,3 & 4 [point to screen]I want you to select one card at a time, by clicking on the card, from any deck that you choose
2. Each time you select a card from a deck, the computer will tell you that you have won some money [point to screen]
3. Every time you win, the green bar gets bigger and your money increases in dollars [point to screen]
4. Every so often, however, when you click on a card, the computer tells you that you have won some money, but then it says that you have also lost some money as a penalty [point to screen]
5. The aim is to win as much money as possible, and if you are unable to win, make sure you avoid losing money.
6. Every time you lose, the green bar gets shorter and your total money goes down [point to screen]
7. You must keep playing until the computer stops
8. You will get \$2000 credit to start the game [point to screen]
9. At the end, you will see how much money you have won or lost.
10. The computer does not make you lose money at random.

Do you have any questions?

You can begin by selecting your first card.